EXAMINATION OF THE ASSOCIATION BETWEEN DIABETES, DEPRESSION, AND SUICIDALITY WITH A SPECIAL FOCUS ON THE INDIGENOUS CANADIAN POPULATION

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ABSTRACT

Diabetes, depression and suicidal behavior are increasingly prevalent conditions with major public health implications. A potential association between these conditions has been suggested in the literature but not entirely explored. The Indigenous Canadian population is facing a growing epidemic of diabetes, depression and suicidal behavior. Yet, this vulnerable population is consistently under-represented in research that addresses mental health issues among patients with diabetes. Therefore, this thesis aimed to: (a) systematically evaluate the association between diabetes, depression, and suicidal behavior among the general population; and (b) assess the inter-relationship between diabetes, depression, and lifetime suicidal ideation among Indigenous Canadians living off-reserve. A systematic literature review and meta-analysis was conducted to examine the associations of interest among the general population. It included 50 studies, 33 assessed depression, 14 suicidality and 3 studies assessed both. Meta-analysis results showed that diabetic patients were at a significantly higher risk of depression compared to non-diabetics. Additionally, patients with diabetes were at a significantly higher risk for experiencing suicidal ideation and attempting suicide. However, there was not enough evidence to support an association between diabetes and suicidal death. Epidemiological modeling of secondary data from the Aboriginal Peoples Survey was used to examine the associations of interest among the Indigenous Canadian population. The prevalence of depressive symptoms in the Indigenous diabetics was 15.67% compared to 9.27% among the non-diabetic participants. After controlling for socio-demographics, smoking/alcohol use/drug use, anxiety disorders and other chronic illnesses diabetes was still significantly associated with depressive symptoms. The prevalence of suicidal ideation in diabetics was 23.86% compared to 18.71% among the non-diabetic participants. After adjusting for the effect of socio-demographics and health related behavioral factors, diabetes was still significantly associated with a higher risk of reporting suicidal ideation. However, after further adjusting for mental disorders (mood and anxiety) and other chronic illnesses, the association was no longer significant. The increased risk of depression and suicidality in diabetic patients among Indigenous peoples and the wider population highlights the importance of integrating the screening and management of depression and suicidal behavior with diabetes management in primary healthcare settings.

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LIST OF ABBREVIATIONS

WHO	World Health Organization
ICD-10	The International Classification of Diseases, Tenth Revision
DSM	Diagnostic and Statistical Manual of Mental Health
PHQ-9	Patient Health Questionnaire
HADS	Hospital Anxiety and Depression Scale
OECD	Organization for Economic Co-operation and Development
NOS	Newcastle Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
APS	Aboriginal Peoples Survey

CHAPTER 1 - INTRODUCTION

This introductory section provides background information on depression, suicidality, and diabetes both in regards to the general and Indigenous populations. It also discusses the main concept of this thesis, specifically as it pertains to the association between diabetes, depression and suicidality within the general and Indigenous Canadian context. In addition, it outlines the main objectives of this thesis work and discusses its significance to the field of public health.

1.1 Background

1.1.1 Depression

Depression is a mood disorder characterized by sadness, loss of interest or pleasure, feelings of guilt or worthlessness, disturbed sleep or appetite, decreased energy, and poor concentration (1). Depression can be long standing or recurrent, substantially impairing an individual's ability to function at work or school or cope with daily life. If severe, depression can lead to suicide (1).

Depression is a relatively common and increasingly more prevalent mental health disorder. In 2017, the World Health Organization (WHO) estimated that more than 322 million (4.4%) people suffered from depression worldwide. Depression is associated with significant economic costs due to loss of occupational productivity, use of medical treatments and healthcare services and suicide related expenditures. It is ranked as the leading cause of global disability at 7.5% and plays a major role in suicide deaths (1). In Canada, 11.3% of adults met the criteria for being diagnosed with major depression, at some point in their lifetime, and 4.7% during the last 12 month (2). Besides the high prevalence, depression accounts for 6.9% of all years lived with disability in Canada (1)

Generally, different clinical terms and classifications have been used for depression. The terms that have been used interchangeably to describe depression include: depressive disorders, major depressive disorder, unipolar depression, clinical depression, depressive episode, and depressive

symptoms. The classifications that have been used in this thesis include: The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) (3) and the American Psychiatric Association Diagnostic and Statistical Manual of Mental Health (DSM-V) (4).

In DSM-V, major depression is defined as depressed mood or loss of interest/pleasure (anhedonia), accompanied by five of the following symptoms: weight change, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, diminished concentration, and recurrent thoughts of death or suicide (4). In ICD-10, patient must have at least two of the core symptoms (depressed mood, loss of interest, or reduction in energy), and a minimum of two associated symptoms (loss of self-esteem, inappropriate guilt feeling, decreased concentration, change in psychomotor activity, sleep disturbance, changes in appetite with weight changes and recurrent suicidal thoughts) to be diagnosed with depression (3).

Both the DSM-V and ICD-10 diagnostic systems require symptoms to be present for at least 2-weeks and to result in functional impairment in order to make a diagnosis of major depression. Both systems further classify depressive episodes into mild, moderate and severe depending on the number of symptoms, extent of social and occupational impairment, and interference with daily life (3, 4). These classifications are typically used during a standard diagnostic interview with a healthcare professional. Consequently, using these classifications for rigorous clinical diagnosis could be time consuming and resource exhaustive.

Given the growing interest in depression research, there is a need to streamline and simplify how depression is defined and diagnosed. Therefore, there is an increased acceptability in the use of self-report questionnaires that measure depressive symptoms such as the Patient Health Questionnaire (PHQ-9) or the Hospital Anxiety and Depression Scale **(**HADS) (5, 6). These tools are based on symptom counts and assume that different symptoms weigh equally, ignoring the pattern of depressive symptoms. Furthermore, they fail to account for variations in duration and the degree of functional impairment (7). Despite these drawbacks, they are still considered to provide good measures of the severity of depression, which has been proportionally related to the number of symptoms (8). Moreover, the use of these questionnaires could prove useful for the categorization of subclinical depressive symptoms, which refers to a depression that doesn't fully

meet the previously detailed clinical criteria of major depression. This category of depression has been associated with significant morbidity and economic costs and represents a risk factor for major depression (9).

In addition to self-report questionnaires, researchers have also used prescription of antidepressant medications in order to help evaluate the presence of depression, especially in light of advances and use of administrative healthcare data in research settings. This method may enable data collection on large samples at lower costs, but it inevitably introduces some bias. Many patients with depressive disorders may not receive pharmacological treatment (10). Whereas, antidepressant drugs are prescribed for conditions other than depression (e.g. long-term pain, anxiety and obsessive compulsive disorders).

1.1.2 Suicidality

Suicide[1] represents a public health emergency worldwide (11). Globally, there are nearly 800,000 suicidal deaths every year, accounting for 1.4% of all deaths. This number is projected to steadily increase through 2030 (12, 13). In Canada, the problem is equally acute with approximately 4,400 suicides reported annually, making it the ninth leading cause of death (14). However, accurate accounts of suicide as a cause of death and reporting suicidal attempts are difficult to confirm because of the social stigma associated with suicide (15). Consequently, the numbers reported most likely underestimate the actual extent of the problem of suicidality.

Estimating the prevalence of suicidal ideation and attempts has proven to be challenging, as rates vary widely in different populations and settings, and largely depend on the evaluation methods used (16). One epidemiological study assessed data from 17 countries and reported a 9.2% lifetime prevalence of suicidal ideation and 2.7% for suicidal attempts. They also observed that 60% of suicide ideators progressed to attempts within a 12-month period after ideation onset (17). Another large study among the Chinese general population reported an estimate for lifetime prevalence of suicidal ideation and attempts to be 3.9% and 0.8%, respectively (18). In Canada,

[1] In this thesis, the term "suicidality" and "suicidal behavior" are used interchangeably to refer to suicidal ideation, suicidal attempts, and suicidal death.

12.1% of those 15 years or older reported having suicidal thoughts in 2015 (19).

Mental health disorders are a known risk factor of suicide death (20). In general, more than 90% of suicidal deaths are associated with mental health disorders (21). Some of the most commonly associated mental health illnesses include: major depression, bipolar disorders, post-traumatic stress disorders, and drug abuse. Psychological predictors of suicide risk include: depressed mood, hopelessness, and impulsivity, with the later acting as a facilitator for the progression from ideation to attempt (22- 24).

1.1.3 Diabetes

Diabetes mellitus is a group of metabolic disorders characterized by chronic elevation in blood glucose (hyperglycemia) due to defects in insulin secretion, action, or both (25). It is traditionally classified into: type 1, type 2, gestational, and other genetic forms of diabetes mellitus (25). In this thesis, we will focus mainly on type 1 and type 2 diabetes.

Type 1 diabetes typically affects younger age groups, mostly children and adolescents, and it is characterized by autoimmune destruction of insulin producing cells leading to insulin deficiency (26). Type 1 diabetes constitutes 5-10% of all diabetic patients and requires regular, daily insulin injections, monitoring of blood glucose and a healthy lifestyle to control blood glucose levels. On the other hand, Type 2 diabetes is the most common type of diabetes and accounts for 90% of all diabetic patients. It usually affects adults and it is due to insulin resistance. Historically, type 2 diabetes is predominantly seen among adults. However, in recent years it has also been observed at an increasing rate among children and adolescents, mostly due to their high rates of obesity, sedentary lifestyle and unhealthy diet.

Typically, type 2 diabetes among adults has been strongly linked to a number of risk factors including: obesity, aging, ethnicity, and family history (26). The critical step in the management of type 2 diabetes is for the patients to adopt a healthy lifestyle and maintain a healthy body weight. In more advanced cases, diabetics are required to take oral hypoglycemic agents and/or insulin to control their blood glucose levels (26).

Hyperglycemia, the hallmark of diabetes, is the leading cause of long-term damage to a number of body organ systems that can broadly be subdivided on the basis of the micro and macro vascular complications of diabetes. Micro vascular complications affect the eyes (diabetic retinopathy), kidneys (nephropathy) and nerves (neuropathy), while the macro vascular complications are mainly linked to an increased risk for cardiovascular diseases (stroke, coronary artery disease, and peripheral vascular disease). Therefore, the micro and macro vascular complications of diabetes are known to have the potential to cause blindness, kidney failure, amputations, and cardiovascular diseases (27).

In 2017, the International Diabetes Federation reported that there were 425 million (8.8%) diabetics worldwide. The number of diabetics is projected to increase by 48%, reaching 679 million people (9.9%) by 2045 with the majority of patients between the ages of 20-64 years old (76.9%) (25). In 2017, more than 5 million deaths were attributable to diabetes, accounting for 10.7% of all global causes of mortality (26). In Canada, there were 3.4 million diabetics (9.3%) in 2015 and the number is expected to increase by 44% and reach 5 million people (12.1%) by 2025 (28). In Canada, the situation is particularly dire, when one considers that it has the third highest rate of mortality due to diabetes among OECD[2] countries with 18 deaths per 100,000 population (29).

Diabetes and its medical complications place a significant economic burden on individual patients, their families and national healthcare systems worldwide. The chronic nature of diabetes and its complications cause substantial direct (mainly for hospital and institutional care, primary care, and medications) and indirect costs (due to premature death and long term disability) (30). Overall, there has been a remarkable increase in the estimates of healthcare expenditure on diabetes from $232 billion United States Dollars (USD) in 2007 to $727 billion USD in 2017 (26). In 2017, Canada was ranked among the top 10 countries worldwide in terms of total healthcare

[2] The Organization for Economic Co-operation and Development (OECD) is an intergovernmental economic organization with 36 member countries, founded in 1961 to stimulate economic progress and world trade. It includes: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States.

expenditure on diabetes by spending a reported $15 billion International Dollars[3] (ID) and having a mean healthcare expenditure per person with diabetes at $5,718 ID (26).

1.1.4 Depression, Suicidality, and Diabetes

Diabetes is a comprehensive disease that is not only associated with physical morbidities but also with psychological ones (31). There is strong evidence to suggest that the prevalence of depression among diabetic patients is significantly higher compared to non-diabetics (32- 34). In a previous meta-analysis, the odds of depression in the diabetes group were two times higher than the non-diabetes group (32). Other studies have also confirmed the higher risk of depression among patients with diabetes (34). Depression significantly impacts the health of diabetic patients leading to poor self-care, non-adherence to medical treatment, reduced quality of life, higher rates of morbidity and mortality, and consequently, increased healthcare costs (33, 35).

Several plausible explanations have been proposed to account for the high co-morbidity between diabetes and depression, and these include: (a) the commonality of environmental factors such as low socio-economic status, which is known to play a role in the progression of both diabetes and depression (36, 37); (b) the role of hyperglycemia and its link to activation of the Hypothalamic–Pituitary Adrenal (HPA) axis, which in turn may predispose to depression (38); (c) the similarities in the changes of the cerebral structure and blood flow that have been observed in patients with diabetes and depression (39, 40); (d) the chronic inflammation and production of inflammatory cytokines, a key feature of diabetes, which are also known to play a role in the development and progression of depression (41); and (e) the use of different diabetic medications that are reported to have a differential effect on the risk of diabetic patients potentially developing depression (42, 43).

Depressive symptoms, especially hopelessness, may increase the risk of suicidal ideations in diabetic patients (44). Suicidal ideation has also been linked to lack of compliance with medical treatment, especially among diabetic patients (44). Although the association between diabetes and depression has been extensively examined in the literature, the association of diabetes with

[3] The International Dollar is a hypothetical unit of currency that has the same purchasing power parity that the U.S. dollar had in the United States at a given point of time.

suicidal behavior remains unclear and evidence at times can be conflicting (45- 48). For example, most studies of suicidal ideations in patients with diabetes focused on young adults with type 1 diabetes and found an increased prevalence of suicidal ideation relative to the general population (45, 46). However, among studies with older individuals suffering from type 2 diabetes, the results have been less consistent (47, 48).

A multitude of factors play an important role in the intricately complex association between diabetes, depression and suicidality. Some of the general risk factors of depression pertain to diabetic patients such as female sex, young age, being single, and low socio-economic status (49). Moreover, some risk factors related to diabetes are known to increase the *risk of depression: (a) the presence of diabetic complications, especially diabetic neuropathy (50, 51), and (b) being treated with insulin, which is a marker for the progression of diabetes (52).

1.1.5 Indigenous Peoples

The United Nations estimates that there are 370 million "Indigenous people[4]" residing in 70 countries across the world and most notably in the Americas, Northern Europe, Australia, and New Zealand. Indigenous peoples (also known as Aboriginal peoples) represent the descendants of native inhabitants of the land before colonization and settlement took place. While there is no existing uniform definition for Indigenous people, they are generally characterized by having a historical continuity with pre-colonial and/or pre-settler societies with distinct social, economic and political systems, cultures and beliefs (53).

The Canadian Constitution Act of 1982 (section 35) states that Indigenous peoples of Canada include: First Nations (58.3%), Métis (35.1%), and Inuit (3.9%) peoples (54). First Nations are recognized as the original inhabitants of the land of Canada. They represent a diverse group with more than 600 First Nations bands and around 60 different languages (55). Almost three-in-four First Nations identify as being Registered Indians (according to the *Indian Act* of Canada) (54).

[4] In this thesis, the term "Indigenous people" and "Aboriginal people" are used interchangeably.

Of all First Nations peoples, 38% live on-reserve[5] and the remaining portion (62%) live off-reserve mainly in major urban settings across Canada (56). Métis people trace their ancestry to a mixed European and Indigenous origin and progressed to develop their own culture and traditions. Inuit people are known to inhabit the northern regions of Canada. The Inuit home is known as "Inuit Nunangat", a term that refers to the land, water and ice in the Arctic region (55).

In 2016, there were approximately 1.7 million people who self-identified as Aboriginal, accounting for 4.9% of the total Canadian population (54). In general, they are considered to be the youngest and fastest growing sub-segment of the Canadian population. The growth rate between 2006 and 2011 was quite remarkable with reports stating that the Indigenous population was increasing at a rate four times higher than the one observed for their non-Indigenous counterparts (20% vs. 5%) (57). The Indigenous population is also known to be significantly younger than the non-Indigenous, with a median age of 28 years old compared to 41 years old for the non-Indigenous population. This age difference is partially explained by the higher fertility rates and shorter life expectancy for the Indigenous peoples in Canada (58).

The Indigenous Canadian peoples are known to generally have a poorer health profile compared to the non-Indigenous Canadian population. They have significantly higher rates of chronic diseases including diabetes and mental health disorders (59). Several factors have been implicated in the health disparities observed among the Indigenous population, including: (a) socioeconomic inequalities, (b) unfavorable physical environmental conditions, and (c) significant barriers to accessing healthcare services (60).

Socio-economic inequities have been reported among Indigenous peoples in Canada with regard to lower income, incomplete education, and higher rates of unemployment. In 2011, the National Household Survey showed that the overall after-tax median income for Indigenous people was $20,000 Canadian Dollars (CAD) compared to $27,000 CAD for their non-Indigenous counterparts (61). Moreover, the proportion of persons aged 25-64 years old, who reported not

[5] Under the Indian Act, an "Indian Reserve" is defined as "land held by the Crown "for the use and benefit of the respective bands for which they were set apart" under treaties or other agreements. Reserves used as residences are referred to as 'Indian Bands'. The reserve system is connected to First Nations peoples who identify as Registered Indians. Inuit and Métis people typically do not live on-reserves.

having an educational certificate, diploma or degree was 29% in Indigenous people, whereas in non-Indigenous people was 12% (62). Employment statistics were equally disconcerting and showed that only 57.1% First Nations, 58.6% Inuit, and 71.2% Métis were employed compared to 75.8% of non-Indigenous people (63).

Indigenous peoples face challenging physical environmental conditions in Canada. In 2016, 19.4% of the Indigenous people reported living in a house that was in need of major repairs compared to only 6% of the non-Indigenous population (64). Significant barriers to accessing healthcare services have also been observed, especially among remote, rural and on-reserve communities, who also lack access to and experience difficulties in communicating with healthcare providers in a timely manner (60).

Finally, systemic racism, social injustices and the institutionalization of practices (e.g. residential schools) that undermine indigenous cultures and values have had a pernicious and persistent effect on Indigenous health (65). Perhaps the best example is illustrated by the aggressive assimilation of Indigenous children, who were removed from their families, communities and cultures and were forced to attendant government sponsored residential schools run by the Christian churches in Canada. It is believed that more than 150,000 Indigenous children attended these schools between the time periods of the mid-1870s to mid-1990s (66). In the process, this experience not only negatively impacted the mental and physical health of the survivors of these residential schools but also that of their descendants, leading to inter-generational trauma (67)

1.1.6 Diabetes and Mental Illness in Indigenous People

Diabetes and mental illness were not known conditions among Indigenous Canadian people (68). Colonization and assimilation resulted in significant changes to the food consumption habits, social environment and economic structure of the Indigenous peoples. These changes were associated with limited access to traditional food resources, loss of culture, erosion of traditional practices and the undermining of the holistic approach to health by Indigenous peoples. This set of prevailing conditions predisposed the Indigenous Canadian peoples to develop new illnesses including the emergence of epidemics in diabetes and mental health illness (68).

Diabetes is a widely prevalent chronic condition among the Indigenous Canadian peoples. The Public Health Agency of Canada (PHAC) reported age standardized prevalence rates for diabetes of 17.2% among First Nations living on-reserve, 10.3% off-reserve and 7.3% among Métis, compared to 5% in the general population (69). Among the Indigenous Canadian population, diabetes (especially type 2) increasingly affects younger age groups and in particular, children and adolescents. It is estimated that the prevalence of type 2 diabetes is nearly 11% among First Nations children, younger than 10 years old (70). If one takes into consideration the early onset of diabetes and its longer exposure to hyperglycemia, it is not surprising to find that diabetes is associated with higher rates of co-morbidities and complications in Indigenous peoples (71).

Indigenous Canadian populations have some of the highest suicide rates worldwide. First Nations experience suicide rates that are two-times the national average and those observed among the Inuit population are even higher, at 6 to 11-times (72). In 2012, 24% of First Nations living off-reserve, 23.5% of Inuit and 19.6% of Métis people reported having lifetime suicidal thoughts, compared to 11.1% in the general Canadian population (73).

Historical social injustices with the subsequent struggles of the Indigenous Canadian peoples, represented in the loss of land, lack of self-governance, discrimination, marginalization, and residential schools (65), made an indelible impact on their lives and led to serious detrimental effects on their mental health. Elias et al. examined suicidal behavior among residential school survivors and their off-spring and determined that both suicidal ideation and suicidal attempts were consistently associated with the history of abuse even for non-attendees, supporting the evidence for an intergenerational traumatic effect (67).

The limited data suggest that the Indigenous Canadian people experience greater rates of depression relative to non-Indigenous population. Data from national surveys show that Indigenous people living off-reserve were 1.8 times more likely to experience depressive episodes in the past year compared to non-Indigenous people (74). Another survey assessing major depression among First Nations living on-reserves found that 14% had major depression, compared to 8% of the general Canadian population (72). However, examination of the literature revealed a significant gap in recent and updated health information available for depression

among First Nations, Métis, and Inuit peoples.

1.1.7 Depression and Suicidality among Diabetic Indigenous Peoples

Most Indigenous focused research is dedicated to health status and life style behavior. In general, there is a shortage of research assessing other aspects of Indigenous peoples' health (75). In Canada, Barton et al., assessed health related quality of life and found that Indigenous participants reported lower scores than non-Indigenous and diabetes was more prevalent among Indigenous (76). With the overall scarcity of Canadian research assessing mental health in Indigenous diabetic patients, Australian studies have taken the lead in exploring this important research topic in recent years. Davis et al. evaluated the prevalence of depression between urban Indigenous and Anglo-Celtic diabetic patients and showed that the prevalence of depression in Indigenous participants was double that of the Anglo-Celtic. Furthermore, among Indigenous participants, depression tended to be major and untreated (77).

It has also been suggested that Indigenous diabetic patients are under-screened for depression in primary healthcare settings. A previous study evaluated depression among Indigenous individuals in primary healthcare settings and concluded that overall, there was a lack of attention to screening and evaluating depression, especially among those patients with more severe disease or poor physical health, as often seen with Indigenous people. The authors explained this finding by using the theory of competing demands, whereby physical illnesses exert strong competition and take precedent over the screening and initiation of mental health care including depression (78). However, there is also the possibility of institutional and systemic racism that leads to disparate treatment within the healthcare setting on the basis of patients' socio-cultural differences and in turn, creates issues of trust and acceptance of mental health services by Indigenous patients (79).

1.2 The problem

The link between diabetes, depression and suicidality has not been fully explored and the limited research in this important area provides evidence that is unclear and at times, conflicting. There is a significant gap in the literature regarding the systematic review and assessment of suicidality in

patients with diabetes and a real public health need to accurately estimate its prevalence among diabetic individuals.

The Canadian literature on the relationship between diabetes and mental health in Indigenous peoples is scarce. There is marked shortage in our collective knowledge regarding the extent of the problem of depression and suicidality among our diabetic Indigenous Canadian peoples. Therefore, this thesis has a two-fold aim: (1) to systematically evaluate the association between diabetes, depression, and suicidal behavior among the general population; and (2) to assess that inter-relationship between diabetes, depression, and lifetime suicidal ideation among Indigenous Canadians living off-reserve.

1.3 Objectives

The main objectives of this thesis are:

1) To conduct a systematic review, synthesis and meta-analysis of the evidence among diabetic patients in order to:
   (a) Assess the risk of depression;
   (b) Estimate the prevalence of suicidal ideations, attempted suicide, and completed suicide;
   (c) Evaluate the association between suicidality and diabetes.

2) To use data from the Indigenous Peoples Survey to:
   (a) Determine the prevalence of depressive symptoms and suicidal ideation among Indigenous Canadian patients with diabetes;
   (b) Investigate whether diabetes is associated with higher risk of depression and suicidal ideation;
   (c) Assess whether that association varies by different risk factors among the Indigenous Canadian populations living off-reserve.

1.4 Relevance

An association between diabetes, depression and suicidality would suggest the need to design and implement culturally appropriate and comprehensive health promotion initiatives among this marginalized population to help reduce and prevent their increased vulnerability for depression and suicidality. The findings of the present study can help guide efforts for best practices in the early detection and effective screening of depression and suicidality among diabetic patients in primary healthcare settings.

1.5 Significance

This study is of great significance to both the general and Indigenous Canadian population. There is a significant gap in literature that methodically assesses suicidality in patients with diabetes. Moreover, the Indigenous Canadian population has consistently demonstrated a higher prevalence of diabetes and depression, suicidal ideation and suicidal attempts. However, there is scarcity of research in this important area that sheds light by investigating these relationships among the Indigenous Canadian peoples.

1.6 Conclusion

Diabetic Indigenous experience significant challenges that increase their risk for depression, suicidal ideation and suicidal attempts. Depression is a known co-morbidity for diabetes and it is oftentimes undiagnosed. This is unfortunate, because currently many effective treatment strategies exist for depression that can make a significant relevant difference in the lives of those affected. Early treatment for depression may help curb the epidemic of suicidal ideation and suicidal attempts among Indigenous peoples suffering from diabetes.

Establishing a better understanding of the risk profile of diabetic patients in general and those of Indigenous descent in particular, can prove useful in properly assessing cases of depression and suicide ideation and help reduce the rates of suicide attempts and suicides in Canada. The

findings of this study help to highlight the importance of integrating the evaluation and treatment of depression with diabetes management in primary healthcare settings and better inform future policy and health promotion initiatives to d screen, diagnose and treat high-risk individuals leading to improved health and better quality of life.

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CHAPTER 2 - RISK OF DEPRESSION AND SUICIDALITY AMONG DIABETIC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 Abstract

Background and Rationale: Depression is commonly seen among diabetics and negatively impacts their compliance with medical treatment, quality of life, morbidity and mortality. Suicidality (suicidal ideation, suicide attempts, and completed suicide) has also been reported to be more prevalent among diabetics. The purpose of this study is to conduct a systematic review and meta-analysis to evaluate the risk of depression and suicidality among diabetic patients.
Methods: Medline, PubMed, EMBASE, Cochrane library, and Psych INFO were searched for studies published from 2008 onwards. Two reviewers assessed the eligibility of each study based on pre-specified inclusion criteria. Meta-analysis was conducted to estimate the pooled effect size. Sources of heterogeneity were investigated through subgroup analysis and meta-regression. Publication bias was assessed using funnel plot and Egger's test.
Results: A total of 5,750 articles were identified and of those, 17 studies focusing on suicidality and 36 on depression were included in this study. Our analysis suggests a positive relationship between diabetes and depression. The pooled OR based on cohort studies was 1.49 (95% CI: 1.36-1.64) and for cross-sectional studies was 2.04 (95% CI, 1.73-2.42). The prevalence of suicidal ideation, attempts, and completed suicide was 16.2%, 2.7%, and 0.3%, respectively. Pooled OR for suicidal ideation, attempted, and completed suicide was 1.89 (95% CI: 1.36- 2.63), 1.45 (95% CI: 1.07- 1.96), and 1.85 (95% CI: 0.97-3.52), respectively. All findings were statistically significant except for completed suicide.
Conclusion: The increased risk of depression and suicidality in diabetic patients highlights the importance of integrating the evaluation and treatment of depression with diabetes management in primary healthcare settings. Further studies are needed to confirm results from this meta-analysis.

Keywords: Diabetes; Depression; Suicide; Suicidal ideation; Suicidal attempts; Suicidal death

2.2 Introduction

Diabetes is considered one of the largest global epidemics and constitutes a public health emergency in many countries (1). The global prevalence of diabetes among adults has nearly doubled in the last couple of decades, rising from 4.7% in 1980 to 8.5% in 2014, resulting in approximately 1.6 million deaths, annually (2). Diabetes is psychologically demanding given the chronic and large burden placed on diabetics for the self-management of their disease. Diabetic patients face several psychological challenges as a result of their illness, which may include: adherence to medical treatment and lifestyle modifications, need for continued monitoring for glycemic control, concerns for complications and disabilities, interference of symptoms with daily activities and psychosocial difficulties at personal and interpersonal levels (3), all of which may eventually lead to depression and in some cases suicide.

Depression is a common mental illness that negatively impacts productivity and quality of life (4). It is reported that patients with depression die 5-10 years earlier than those without depression (5). Evidence suggests that the co-morbidity of depression and diabetes is relatively common (6, 7, 8). A previous meta-analysis estimated the prevalence of depression to be twice as high among diabetics compared to the general population (6). Other systematic reviews corroborated these findings and demonstrated a significantly higher risk for diabetic patients to develop depression compared to non-diabetics (7, 8).

The co-morbidity between diabetes and depression is associated with poorer prognosis and higher medical expenditures than either condition alone (9). This is an expected finding as depression significantly impacts diabetic patients leading to poor self-care, non-adherence to medical treatment, reduced quality of life, higher rates of morbidity and mortality, and consequently, increased healthcare costs (10, 11). Additionally, depression among diabetic patients tends to last longer and has higher recurrence rates compared to non-diabetics (12). Consequently, identification of depression among diabetic patients is critically important to mitigate these negative personal consequences and realize cost-savings in healthcare.

Suicide was responsible for more than 800,000 deaths per year in 2015 and is the second leading cause of death among those aged 15 to 29 years old worldwide (13). Depressive symptoms may

increase the risk of diabetic patients displaying suicidality (14), which may include: suicidal ideation, attempted suicide, and completed suicide. Although the association between diabetes and depression has been previously examined, the association with suicidality remains unclear and the evidence is limited and at times, conflicting (15-17).

There is a significant gap in the literature regarding the systematic assessment of depression and suicidality in patients with diabetes. To the best of our knowledge, the present study is one of the first meta-analyses of its kind. The purpose of this study was to conduct a systematic synthesis and meta-analysis of the evidence in order to: (1) assess the risk of depression (including clinical depression, depressive symptoms, and use of antidepressants); (2) determine the prevalence of suicidality; and (3) evaluate the risk of suicidality among diabetic patients.

2.3 Methods

2.3.1 Data sources and search strategies

A systematic literature search was undertaken using five relevant databases: PubMed, Medline, EMBASE, Psych INFO, and Cochrane Library. Search strategies focused on three major domains: (a) diabetes; (b) depression or suicidality; and (c) quantitative outcome measures. A combination of keywords was used for the search and it included the following: ((((("diabetes mellitus"[MeSH Terms]) OR "diabetes mellitus, type 1"[MeSH Terms]) OR "diabetes mellitus, type 2"[MeSH Terms])) AND (((((((("depression"[MeSH Terms]) OR "depressive disorder"[MeSH Terms]) OR depressive symptoms [MeSH Terms]) OR "suicide"[MeSH Terms]) OR "suicide, attempted"[MeSH Terms]) OR suicidal ideation [MeSH Terms]) OR suicide thoughts [MeSH Terms])

2.3.2 Eligibility criteria and study selection

In our study, eligible articles were required to: (a) be published in the English language; in peer-reviewed journals since 2008; and available in full text; (b) assess patients with type 1 and/or type 2 diabetes mellitus, who either self-report a physician diagnosis of diabetes; or were prescribed anti-diabetic medications; or were participants in studies using lab based assessments; and (c) evaluate depressive disorders, or use of antidepressants or depressive symptoms based on

validated standardized questionnaires. Studies were also selected by scanning the reference lists of previous systematic reviews on the topic.

Articles had to have a comparative study design and provide sufficient data to calculate odds ratio for depression among diabetics. For suicidality, single group studies in diabetic patients were eligible for inclusion. Studies that explicitly assessed patients with gestational or genetic forms of diabetes were excluded, as were studies for children younger than 11 years old. Studies were also excluded, if they did not contain sufficient data to estimate the effect size. Eligible articles were identified through title and abstract screening, followed by full text review. Two reviewers, RE and SE, independently evaluated studies for relevance in a standardized manner. Non-agreement was resolved by JM through discussion and adjudication.

2.3.3 Data extraction

Data extraction strategies were developed and pilot-tested on 20 randomly selected included studies and then modified accordingly. Information extracted in duplicate from studies included: author, publication year, country, study design, follow-up time (for cohort studies), settings, total number of participants, age and sex of study participants, method of diabetes evaluation, method of depression or suicidality assessment, reported effect measure with 95% confidence interval, and covariates for adjusted effect measures.

Unadjusted odds ratios and 95% confidence intervals were calculated using the number of events in the exposed and non-exposed groups. Odds ratios for depression were calculated for cohort studies using cumulative incidence in the exposed compared to the non-exposed group. When crude numbers were not available, we used the least adjusted effect measure reported by the authors.

2.3.4 Risk of bias

Two reviewers (RE and SE) independently assessed the validity of eligible studies by using a modified version of the Newcastle Ottawa Scale (NOS) (18). The NOS assesses representativeness of the study sample, comparability between respondents and non-respondents, ascertainment of depression or suicidality, and thoroughness of the reported descriptive statistics.

Studies were rated as having a low, moderate or high risk of bias. Disagreements were resolved by a third reviewer (JM) through consensus.

2.3.5 Data analysis

Statistical analysis was performed using the Comprehensive Meta-analysis software-version 3 (CMA-3) (19). For depression, pooled odds ratios (both adjusted and unadjusted) were the effect measure of interest. While for suicidality, both odds ratios and pooled prevalence among diabetics were the focus of our analysis. As heterogeneity was likely to exist, a random effect model was used to calculate pooled estimates, which allows for estimating both within and between studies variation. We examined heterogeneity using the Cochran's Q heterogeneity test and I^2 as a measure for inconsistency (20).

To investigate possible explanations of heterogeneity, subgroup analysis and meta-regression were conducted. For depression, pre-specified moderator variables included: geographical location of the study, percent of female participants, method of depression evaluation (disorders, symptoms, or antidepressants), whether diabetes was prevalent or incident, comparison group (normo-glycemic or non-diabetic), and risk of bias for each individual study. For suicidality, moderator variables also included: study design, type of diabetes as (type 1, type 2 or not specified), and level of adjustment (no, partial [less than five confounders], or full [greater than five confounders]).

Influential analysis was conducted for the effect of each study on the pooled estimate by reassessing estimates after removal of one study at the time. To visually assess for publication bias, the funnel plot method was used. The Egger's regression intercept method was also used to confirm and statistically test for the bias observed in the funnel plot (21). When publication bias was detected, a Duval and Tweedie trim and fill method was used to calculate the adjusted effect size (22). All analysis used a 5% level of significance (α=0.05).

2.4 Results

2.4.1 Study selection

The PRISMA flow chart depicting the study selection is shown in Figure 2.1. A comprehensive search of the literature yielded a total of 5,750 articles from which 1,733 were removed either for being duplicates or published before 2008. This left 4,018 articles for screening. After initial screening for titles and abstracts, 427 articles qualified for full text screening of which 355 were excluded due to one or more of the following conditions: (a) their full text was not available; (b) were not written in English; (c) focused on special populations; and/or (d) reported inadequate data or mixed outcomes. In total, 50 studies were analyzed, with 33 reporting data only on depression, 14 only on suicidality, and three studies reporting data on both depression and suicidality among diabetic patients (23, 24, 25).

2.4.2 Risk of Bias

All cohort studies assessing depression among diabetic patients were classified as either low or moderate in terms of the risk of bias except for one study, which was classified as having a high risk of bias. Among cross-sectional studies assessing depression, seven were classified as low risk of bias, 15 were moderate and two studies had a high risk of bias. For studies assessing suicidality, 14 were rated as having low risk of bias, 11 moderate, and one as high risk of bias.

2.4.3 Study Characteristics

3.1 Depression

Depression studies were stratified and examined on the bases of their study design. Table 2.1 and 2.2 include summary of the characteristics of depression studies included in the review

A. Cohort studies

There were 12 cohort studies included for depression. One study (26) reported two datasets for patients with prevalent and incident diabetes, leaving a total of 13 datasets for analysis. Three studies (27, 28, 29) used incident prescription of antidepressants as a proxy for depression diagnosis, five studies (26, 30, 31, 32, 33) used clinical diagnostic criteria, and three (34, 35, 36)

relied on questionnaires. One study used both questionnaires and prescription of antidepressants (34). Follow-up period ranged from two (26) to 15 years (28). Most studies were from Europe or North America while only two studies were from Asia (30, 31). Ascertainment of diabetes was made by physician diagnosis (ICD code) (26, 28, 30, 31, 32, 35), use of anti-diabetic medications (27, 29, 35), self-reported diagnosis of diabetes (36, 37), and/or lab assessment (34, 35).

B. Cross-sectional studies

There were 23 cross-sectional studies and one case-control study (38) on depression and diabetes. Additionally, three of these studies reported data on suicidality (23, 24, 25). Depression was evaluated by: (a) questionnaires; (b) clinical diagnostic criteria (9 studies) (38, 39, 40, 51, 23, 42, 43, 44, 24); and (c) utilization of antidepressants (one study) (45). Two studies (39, 41) used both depressive disorders and symptoms but for the analysis we used only results for depressive disorders.

3.2 Suicidality

Suicidality was stratified and examined on the bases of outcome. Table 2.3 and 2.4 include summary of the characteristics of suicidality studies included in the review

A. Completed suicide

Seven studies reported data on completed suicide (all cohort). Suicidal death was confirmed by either ICD codes or examination of death certificate.

B. Suicidal attempts

Five studies assessed suicidal attempts and self-harm (one cohort, one nested case-control and three cross-sectional). Attempted suicide was evaluated based on either ICD codes or self-reported information.

C. Suicidal ideation

Twelve cross-sectional studies examined suicidal ideation. Three of them evaluated type 1 diabetics, one study evaluated type 2 diabetic patients, who were on insulin (24), while the remaining studies included both type 1 and type 2 patients. Two studies had minors as

participants (adolescents) (17, 46). All studies used self-reported information to evaluate for the presence of suicidal ideation.

2.4.4 Main meta-analysis results

4.1 Depression

Depression results are reported as odds ratios (adjusted and unadjusted) by study design.
The overall OR based on all depression studies (cohort and cross-sectional) was 1.79 (95% CI: 1.62-1.99), with significant heterogeneity (I^2= 98.09%, Q-value= 9.66, and p-value < 0.001). Estimated odds ratios for the cohort and cross-sectional studies were significantly different (p-value=0.002).

A. Cohort studies

The pooled unadjusted odds ratio for the association between diabetes and depression calculated based on all 13 studies, using a random effect model was 1.49 (95% CI: 1.36-1.64, p-value <0.001). Forest plot of the OR and 95% CI for the random effect model are shown in Figure 2.2. There was significant heterogeneity between studies (I^2= 94.08%, Q= 203.12, p-value < 0.001). All standardized residuals were between the values of 3 and -3, suggesting no potential outliers. The pooled adjusted effect estimate was calculated based on 5 studies (27, 34, 35, 36, 37) with an OR= 1.48 (95% CI: 1.16-1.88) and p-value= 0.001. The test for heterogeneity was not significant (I^2=54.2%, Q= 8.73, p-value= 0.068).

B. Cross-sectional studies

Unadjusted odds ratio for depression among diabetics, calculated based on cross-sectional studies was 2.04 (95% CI: 1.73-2.42) p-value <0.001. However, there was a significant heterogeneity (I^2=93.79%, Q= 370.7, p-value < 0.001). Adjusted odds ratio from cross-sectional studies was 1.67 (95% CI: 1.47-1.90) p-value <0.001, with significant heterogeneity (I^2=74.16%, Q=58.05, p-value < 0.001).

4.2 Suicidality

Suicidality results are reported as prevalence and odds ratios (adjusted and unadjusted) stratified by outcome.

A. Completed suicide

Overall prevalence was 0.3% (95% CI: 0.1 – 0.7%). Based on the five included studies (47, 48, 49, 50, 51), the unadjusted pooled odds ratio was 1.85 (95% CI: 0.97- 3.52, p-value= 0.061) (Figure 3.2), with significant heterogeneity (I^2= 94.79%, Q-value= 76.88, p-value <0.001). Adjusted OR (based on three studies) was 1.39 (95% CI: 0.82-2.35, p-value 0.225) (I^2= 81.66%, Q= 10.90, p-value= 0.004).

B. Suicidal attempts

The pooled prevalence of attempted suicide was 2.7% (95% CI: 0.9 – 7.8%). Three studies reported unadjusted odds ratios. The calculated unadjusted pooled odds ratio was 1.45 (95% CI: 1.07-1.96, p-value= 0.017) (Figure 3.2), with significant heterogeneity (I^2= 53.43%, Q= 4.29, p-value= 0.117). Adjusted odds ratio based on two studies (23, 52) was 1.33 (95% CI: 1.09-1.62, p-value=0.005) (I^2=0%, Q= 0.23, p-value= 0.635).

C. Suicidal ideation

The prevalence of suicidal ideation, among diabetics was 16.2% (95% CI: 8.5 - 28.5%). Unadjusted pooled odds ratio (based on six studies) was 1.89 (95% CI: 1.36- 2.63, p-value <0.001) (Figure 3.2), with significant heterogeneity (I^2= 94.09%, Q-value= 84.65, p-value<0.0001). One study (24) had high-standardized residual (of 3.36), so it was considered as an outlier. After exclusion of this study, heterogeneity improved (I^2 was reduced to 63.7%), but it remained significant (p-value= 0.026), and the new pooled estimate for suicidal ideation was 1.49 (95% CI: 1.40, 1.60). Adjusted odds ratio (based on four studies) was 1.49 (95% CI: 1.14-1.96, p-value= 0.004) (I^2= 80.37%, Q= 15.28, p-value= 0.002).

2.4.5 Subgroup analysis and meta-regression

5.1 Depression

A. Cohort studies

To explain the significant heterogeneity, several subgroup analyses and meta-regressions were conducted. In the six studies that evaluated depression among diabetics using clinical diagnostic criteria, the pooled OR was 1.59 (95% CI: 1.35-1.86) and the test of heterogeneity was significant (I^2= 88.09%, Q=41.98, p-value <0.001). In the four studies that evaluated depression among diabetics using questionnaires, the pooled OR was 1.41 (95% CI: 1.17-1.69), while the test of heterogeneity was not significant (I^2=9.24%, Q=3.30, p-value= 0.340). For the three studies that used antidepressants, the pooled OR was 1.36 (95% CI: 1.19-1.54) and test of heterogeneity was significant (I^2=97.32%, Q=74.52, p-value <0.001). Studies were stratified on the basis of assessing patients with incident diabetes OR=1.49 (95% CI: 1.33-1.69) and prevalent diabetes OR=1.47 (95% CI: 1.25-1.72). Other confounders (level of adjustment, comparison group, risk of bias, and geographical location) did not significantly impact the effect estimate. Results for meta-regression are included in Table 2.5.

B. Cross-sectional studies

In evaluating depression, the same pattern observed for cohort studies was maintained in cross-sectional studies. In examining the differences between groups, depressive disorders (OR= 2.24, 95% CI: 1.46-3.45), depressive symptoms (OR=1.47, 95% CI: 1.37-1.57), and antidepressants (OR= 1.89, 95% CI: 1.86-1.92) were not statistically significant (p-value= 0.738).

5.2 Suicidality

The results for suicidality subgroup analysis are included in Table 2.6. Due to the limited number of studies assessing attempted suicide, no subgroup analysis was conducted for that particular outcome.

2.4.6 Influential analysis and publication bias

Influential analysis revealed that no single study had a substantial influence on either the adjusted or unadjusted effect estimates. There was evidence of publication bias for depression among cohort studies based on the inspection of the funnel plot (Figure 2.4) and Egger's test (p-value=0.027). To account for this bias, a Duval and Tweedie test was used and reported an adjusted OR 1.25 (95% CI: 1.15- 1.37). There was no evidence of publication bias for depression among cross-sectional studies (p-value=0.721) and suicidality studies (p-value = 0.860).

2.5 Discussion

To our knowledge, this study is one of the first meta-analyses that reports the prevalence of suicidality among diabetic patients and assesses the association between diabetes, depression, and suicidality using data from observational studies. Our results show that diabetic patients are more likely to have depression, experience suicidal ideations and attempt suicide compared to non-diabetic patients. The findings of this study help highlight diabetics as a high-risk group for depression and suicidality.

In regards to depression, based on 13 cohort studies and 23 cross-sectional studies, our results suggest that there is a significant association between depression and diabetes. It is interesting to note that this association maintained its strength even after adjusting for potential confounders. Previous systematic reviews have shown that patients diagnosed with diabetes are at higher risk for depression (7, 53). Similarly, our analysis of cohort studies corroborates the existing evidence (53) and suggests a directionality, whereby diabetes may play a causal role in the development of depression.

The psychological burden of diabetes may lead to but does not fully account for the increased risk of depression (3). Other potential physiological contributors include: activation of the hypothalamic pituitary adrenal axis (54, 55), chronic inflammation (56) and cerebral vascular changes induced by diabetes (57). Additionally, some common medications used for the treatment of diabetes have been linked to a higher risk of depression (58,59).

In our study, the calculated odds ratio for cross-sectional studies (assessing prevalence of depression) was higher than the one in cohort studies (assessing incidence of depression), corroborating the results reported in a previous meta-analysis (6). This finding may be explained in part by: (a) the longer duration of depression among diabetic patients and (b) the potential bidirectional association between diabetes and depression.

The longer duration of depression among diabetic patients may be due to the increased likelihood to experience treatment resistant and recurrent forms of depression (12). This leads to a build up of chronic cases. The potential bidirectional association between diabetes and depression has also been examined in the literature (34, 60). Depression has been linked to the development of type 2 diabetes with the use of certain antidepressants, which are known to have clinical effects on glucose homeostasis and weight gain (61). Additionally, depression may have a negative effect on a patient's lifestyle choices including physical activity, leading to an increased risk to develop diabetes (62). Thus, it is unsurprising that the risk of prevalent depression was higher than that of incident depression among diabetic patients in our study.

Suicidality among diabetic patients has not been fully elucidated. This study examined the prevalence and risk of suicidality among diabetic patients in order to address the existing gap in the literature. In the general population, a study involving 17 countries found the lifetime prevalence of suicidal ideation and attempts to be at 9.2% and 2.7%, respectively (63). By comparison, our study found that the prevalence of suicidal ideation among patients with diabetes was much higher at a reported 16.2% (95% CI: 8.5 – 28.5%), while the rate of attempted suicide was similar at 2.7% (95% CI: 0.9 – 7.8%).

Depression is one of the leading risk factors for suicidality (14, 64). In our study, diabetic patients were found to be twice as likely to experience suicidal ideations compared to non-diabetics. When examining attempted suicide, diabetics were also significantly at higher risk compared to non-diabetics. These findings are concerning and help highlight the vulnerability of diabetic patients possibly progressing from suicidal ideation to attempted suicide.

In this study, despite the increased risk of suicidal ideation and attempts, diabetic patients did not experience a significant risk of suicidal death (OR=1.85, 95% CI: 0.97- 3.52, p-value= 0.061). This could be attributed to several reasons connected to suicide, including: (a) stigmatization; (b) misclassification; (c) low occurrence; (d) limited details and number of studies; and (e) lack of research into the distinct predictive factors for suicidal death.

Stigma related to suicide is a major barrier in accurately reporting and tracking of suicidal deaths (65). The high level of stigmatization in many countries, where suicide is considered to be immoral and illegal, might lead to underreporting of suicide as a cause of death (66). This in turn would negatively impact accuracy of suicide rates reported in large-scale epidemiological studies (66). Misclassification of suicidal death due to insulin overdoses as accidental death or death due to natural causes is another possibility that need to be further evaluated. Studying suicide is also statistically challenging because of the relative low occurrence of the event and the need for large samples to obtain reliable estimates (67). Additionally, in the present systematic review, the limited number of studies assessing suicidal attempts lacked some key details. For example, there was dearth of information assessing the seriousness of the attempt (i.e. extent of hospital care required afterward or whether the attempt resulted in permanent disabilities). Furthermore, it has been suggested in the literature that suicidal ideations and behaviors might have different predictors than completed suicide (68, 69). Therefore, we cannot fully rely on suicidal ideations to understand completed suicide. Factors that may play a role in moving from one condition to another remain unclear for diabetic patients and need to be carefully investigated.

Strengths and Limitations

This study has several strengths. It provides an up-to-date literature review, which includes both depression and suicidality as outcomes of interest among diabetic patients. It uses best practice methods to help shed light on this very important and under-investigated topic. It provides evidence that can be used as a reference point for future research focusing on specific diabetic sub-populations. Finally, it takes into consideration several important factors (i.e. method of depression evaluation, type of diabetes, whether diabetes was incident or prevalent, and geographical location) in the analysis of our data, which adds to the robustness of this study.

However, there are also several limitations we need to consider. First, there are few studies assessing suicidality, especially attempted suicide. Second, there was a marked heterogeneity among the included studies. Third, we included studies that used prescription of antidepressants as a proxy for depression. This method is quite controversial especially among diabetic patients since antidepressants are commonly used for symptomatic treatment of diabetic neuropathic pain, which may falsely increase reported estimates. However, our subgroup analysis showed that differences in depression evaluation methods did not significantly impact our results. Fourth, confounding bias could not be entirely eliminated. Fifth, association of diabetes and suicidal attempts and suicidal ideation do not imply causation. Finally, most studies included in our systematic review were from developed countries and therefore, the results of our analysis need to be interpreted with caution, as they may not be generalizable to the developing world.

Implications for future research and clinical practice

There are significant gaps and opportunities for research in this important public health topic. Further research is warranted to: (a) examine the factors, mechanisms and transitional triggers implicated in the association between diabetes, depression and suicidality; (b) assess the role and impact of different diabetes management strategies on the patient's risk of depression and suicidality; and (c) evaluate the cultural and ethnic differences as they relate to diabetes, depression and suicidality.

Clinicians should be aware and receive cross-training in order to be better prepared to address the higher risk for depression and suicidality among diabetic patients. Additionally, several other initiatives can be considered, including: (a) early detection and treatment of depression which would improve diabetes control and consequently, delay the development of diabetic and depression related complications; (b) there is a need to develop robust and standardized validated screening tools for diabetic patients at risk for depression and suicidality; and (c) there is an urgency to design and implement comprehensive interventions that take into account the complex inter-relationships between depression and suicidality so as to improve the quality of life of diabetic patients.

2.6 Conclusions

Our study found that diabetes is associated with an increased risk for depression, suicidal ideation and suicidal attempts but not completed suicide. Therefore, efforts for early detection and effective screening are urgently needed in primary care settings. Appropriate training for healthcare providers in the field of suicidality screening and depression management would help mitigate the negative impacts on a diabetic patient's quality of life and reduce the growing burden on healthcare systems. Given the limited number of studies on this important topic, further well-designed studies are needed to confirm the findings of this meta-analysis.

2.7 References

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Table 2.1: Characteristics of selected depression studies

Author &Year	Country	Study Design	Setting	Patients N	Age	Female %	Type of Diabetes	Outcome reported	Evaluation of Outcome
Icks et al, 2013 (35)	Germany	Prospective cohort	Population based, mandatory residence in some cities	3,663	45-75	48.6	Not specified, (included diagnosed, undiagnosed, and IGT)	Depression	CES-D SF (15 items) ≥ 17
Cleal et al, 2017 (28)	Netherland	Prospective cohort	Population registers	3,434,420	18-59	48.9	Not specified Incident diabetes	Depression	Prescription of antidepressants
O'Connor et al, 2009 (26)	USA	Historical cohort 2yrs	Patients enrolled in a health plan, services provided by primary care, family physicians and general internists	2932 with incident diabetes and 14,144 with prevalent diabetes with equal number of matched controls	≥ 40 Mean around 61	47.3%	Not specified but majority were type 2 ICD-9	Depression	ICD-9 ± antidepressants
Chen et al, 2013 (30)	Taiwan	Cohort	National health insurance claims and data linkage		Mean 60.1± 13.2	46.5	Type 2 ICD-9 CM	Depression	ICD-9CM
Hamer et al, 2011 (37)	UK	Prospective cohort	Community dwelling with older adults	4338	Mean 62.9 ± 9	45.2%	Not specified Self report physician diagnosis	Depression	CES-D (8 items) With a cut off ≥4
Hsu et al, 2011 (32)	Taiwan	Cohort Median follow up 6.5 yrs.	Claim data, national health insurance program	14,048 diabetics and 55,608 control	≥20		Not specified (incident diabetes) ICD-9CM	Depression	ICD-9CM
Golden et al, 2008 (34)	USA	Prospective cohort 3.1 yrs.	Part of multi ethnic study of atherosclerosis	4847	45-84		Type 2 FBG ≥126 or on OHA or Insulin	Depression	CED-D ≥16 or use of antidepressant medications or both
Huang et al, 2012 (31)	Taiwan	Prospective cohort 4 yrs.	Service claim records	200,432			Not specified ICD-9-CM	Depression	ICD-9CM

Demakakos et al, 2014 (36)	UK	Prospective cohort	Community dwellings	4,238	≥50		Not specified Self report physician diagnosis	Depression	CES-D (8 items) With a cut off ≥4
Knol et al, 2009 (29)	Netherland	Cohort	Pharmacy registry database	49,593 diabetics and 154,441 non diabetics	>40		Not specified Incident diabetes	Depression	Incident use of antidepressants
Aarts et al, 2010 (33)	Netherland	Retrospective cohort 7.7-7.9 yrs.	General practice patients	6140 and 18416 control	>40 -97 Mean 63.8 ± 11.2	51% among cases and 53% among control	Type 2 ICPC diagnosis based on FBG > 124	Depression	ICPC code through diagnostic interview
Kivimaki et al, 2010 (27)	Finland	Cohort	Employees Record linkage	493 diabetics and 2450 control	25-65	58%	Type 2 Incident diabetes , first diagnosed as eligible to treatment	Depression	Antidepressants
Ryu et al, 2016 (38)	USA	Nested case-control	Electronic health records of primary care patients	Cases with MDD= 11,375 and equal number of controls	Median age 43	65%	Not specified At least two diagnostic codes for the condition >30 days apart	Depression	≥2 MDD-related (ICD-9-CM) diagnosis codes, ≥ 1 anti-depressant prescription, ≥ 1 mention of MDD diagnoses within inpatient or outpatient
Icks et al, 2008 (70)	Germany	Cross-sectional	Baseline data from German Heinz Nixdorf Recall study	2090 diabetic and 4595 non diabetic	45-75	50.2%	Not specified Self report physician diagnosis or medications, or FBG and RBG	Depression	CES-D short form ≥ 15
James et al, 2010 (39)	Nigeria	Cross-sectional	Outpatient clinic in tertiary center	200 cases and 200 control	20-64 Mean 47.1 ± 9.6	54%	Not specified, diagnosed for > 1yr Based on WHO criteria	Depression	SCAN and BDI (21 items) ≥ 10

Bruce et al, 2016 (71)	Australia	Cross-sectional	Prior involvement in Brusselton Health Survey (community based study)	184 cases and a84 controls	Mean 70.2 ± 10.1	50%	Type 2 Self report and FBG	Depression	PHQ-9 and BLDS according to DSM-IV criteria for major and minor depression
Lin et al, 2008 (40)	17 countries	Cross-sectional	Household residing adults	42,697	Mean between 35.8-48.2	Between 47.5%- 55.1%	Not specified Self report physician diagnosis or medications	Depression	CIDI- interview based
Van Doreen et al, 2016 (41)	Netherland	Cross-sectional	Baseline for a population based study	862	Mean 64 ± 7	30% in diabetics and 51% in non diabetics	Type 2 on Insulin or OGTT	Depression	MINI structured interview and PHQ-9 ≥ 10
Foran et al, 2015 (72)	Ireland	Cross-sectional	Part of CLARITY study	283 diabetic and 283 non diabetic	>50 Mean 68± 9.5	41%	Type 2	Depression	HADS-D
Chung et al, 2014 (23)	Korea	Cross-sectional	Population health survey (KNHANES IV, V)	34,056	≥ 20	57.1%	Not specified Self report diagnosis, FBG ≥ 126, current use of anti-diabetic medications	Depression	CIDI-SF
Diaz et al, 2017 (73)	USA	Cross-sectional	NHANES data 2007-2012	7717	≥ 20		Type1 & 2 Self report diagnosis and lab evaluation	Depression	PHQ-9, DSM-IV TR diagnostic criteria
Berg et al, 2012 (45)	Norway	Cross-sectional	Norwegian prescription database	3,434,2333	≥ 20	50.9%	Not specified On anti-diabetic treatment	Depression	Antidepressants
Meurs et al, 2016 (42)	Netherland	Cross-sectional	Lifeline cohort study population	90,686	18-93 Mean 45	59%	Not specified Self reported use of anti-diabetic medication or diagnosis of diabetes	Depression	MINI
Mantyselka et al, 2011 (74)	Finland	Cross-sectional	Based on population survey, subjects	2,712	45-74		Type 2 Self report diagnosis	Depression	BDI ≥ 10 and ≥ 16

Clarke et al, 2016 (43)	UK	Cross-sectional	Scotish family health study	23,690	>18	51.2%	Type 2 Self report diagnosis and medication use	Depression	SCID
Bouwman et al, 2010 (75)	Netherland	Cross-sectional		2667	40-65	46.4%	Type 2 FBG >7 mmol /l or 2hrPG 11.1 mmol/l	Depression	CES-D ≥ 16
Li et al, 2016 (76)	China	Cross-sectional		11,531	≥ 35		Not specified FPG ≥ 7 mmol/l or previous diagnosis by a medical practitioner	Depression	PHQ-9 ≥ 10
Saglam et al, 2010 (77)	Turkey	Cross-sectional	Outpatient diabetes clinic	500 diabetic patients and 90 control	35-65		Type 1& 2 Known diabetics for at least 1 yr.	Depression	BDI (21 items) >13
Kim et al, 2015 (78)	USA	Cross-sectional	NHANES 2007-2008 and 2009-2010	2,266	20-79		Not specified Self report diagnosis	Depression	PHQ-9 ≥ 10
Islam et al, 2015 (79)	Bangladesh	Cross-sectional	Tertiary hospital attendants	591 cases and 591 control	20-60 Mean 50.4 ± 11.4	57%	Not specified Attending physician diagnosis	Depression	PHQ-9 ≥ 10
Wiltink et al, 2014 (80)	Germany	Cross-sectional	Gutenberg health study population	15,010	35-74 Mean 55	50.4%	Not specified Self reported diagnosis and FBG >126 or RBG >200	Depression	PHQ-9 ≥ 10
Bessel et al, 2016 (44)	Brazil	Cross-sectional	Civil servants active or retired	14,447	35-74	54.1%	Not specified Self report diagnosis, medication use, HbA1c, OGTT	Depression	CIS-R clinical interview criteria revised
Adriaanse et al, 2008 (81)	Netherland	Cross-sectional	The Hoorn study population	550	69.5 ± 6.3	49.8%	Type 2 OGTT or on treatment	Depression	CES-D ≥ 16

Westra et al, 2016 (82)	Netherland	Cross sectional		527	60-87	Type 2 WHO criteria, known type 2 and using anti-diabetic medications or diet	Depression	CES-D ≥ 16
Lee et al, 2014 (25)	South Korea	Cross-sectional	KNHANES dataset	9159	≥ 40	Not specified	Depression	Single question
Ceretta et al, 2012 (24)	Brazil	Cross-sectional	Outpatients	994 cases and 2145 controls	>18	Type 2 >5 yrs. On insulin >1yr.	Depression and SI	MINI

Table 2.2: Data from selected studies for systematic review and meta-analysis (depression studies)

Author & Year	Outcome	Total number of diabetic patients	Number of diabetic events	Reported estimate (95% CI)	Adjusted estimate (95% CI)	Adjustments
Icks et al, 2013 (35)	Depression (diagnosed diabetics)	255	18		1 (0.59 – 1.68)	age and sex, BMI, MI, stroke, physical activity, education
Cleal et al, 2017 (28)	Depression	98006	19849			
O'Connor et al, 2009 (26)	Depression	***Prevalent diabetes*** 14144 ***Incident diabetes*** 2932	1117 276		For low visit subjects OR= 1.46 (1.19-1.8)	Age, sex, number of primary care visits
Chen et al, 2013 (30)	Depression	16957	713		HR= 1.43 (1.16-1.77)	Age, sex, geographic area, urbanization statuses, and various comorbidities
Hamer et al, 2011 (37)	Depression				OR= 1.52 (1.01-2.3)	Age, baseline depressive symptoms, sex, smoking, alcohol intake, social status, CRP, Cholesterol, and BMI
Hsu et al, 2011 (32)	Depression	14,048	258	HR=1.79 (1.54-2.07)	HR= 1.46 (1.24-1.71)	Age, sex, occupation and income and comorbidity including hypertension, stroke, hyperlipidemia and coronary artery disease

Golden et al, 2008 (34)	Depression	417	Incidence density 62/1000 for diabetic patients and 37/1000 non diabetics 60 developed depression		OR= 1.52 (1.09-2.12)	Race, ethnicity, exam site, BMI, SES, lifestyle factors, diabetes severity (dyslipidemia, HTN, HTN medications microalbuminuria)
Huang et al, 2012 (31)	Depression	5685	331 (cumulative incidence)	Annual prevalence for diabetics 34/1000 for non diabetics= 11/1000 Cumulative prevalence 92/1000 for diabetics and 41/1000 for non diabetics		
Demakakos et al, 2014 (36)	Depression			OR (52-64 yrs.) = 2.17 (1.33-3.56) OR (> 65 yrs.) = 0.96 (0.59-1.57)	OR (52-64 yrs.) = 1.83 (1.06-3.18) OR (> 65 yrs.) = 0.81 (0.48-1.37)	Age, elevated depressive symptoms at baseline, sex, marital status, education, household wealth, CVS and non CVS comorbidities, BMI health behavior smoking alcohol consumption frequency and physical activity
Knol et al, 2009 (29)	Depression	49593	7631		RR= 1.71 (1.36-2.13)	Age, sex, chronic disease
Aarts et al, 2010 (33)	Depression	6140	122	HR= 1.32 (1.19-1.48)	HR= 1.26 (1.12- 1.42)	Age, practice identification code and depression preceding DM

Kivimaki et al, 2010 (27)	Depression	493	36	OR= 2 (1.57-2.55)		Matching was based on 6 variables: age group, sex, socioeconomic position, type of employment, type of employer, and geographic area workplace
Ryu et al, 2016 (38)	Depression	237	205		OR= 2.8 (1.9-4.1)	Educational level and obesity
Icks et al, 2008 (70)	Depression	352	47		OR (male)= 0.5 (0.27-0.91) OR (female)= 1.14 (0.73-1.76)	Age, co-morbidity, depression induced medications, smoking, activity level, living without a partner, and education
James et al, 2010 (39)	Depression	200	60			
Bruce et al, 2016 (71)	Depression	184	23			
Lin et al, 2008 (40)	Depression			OR=1.38 (1.15-1.66)		Age and gender
Van Doreen et al, 2016 (41)	Depression	253	22		OR= 1.73 (1.38-3.6)	Age, sex and education level
Foran et al, 2015 (72)	Depression	283	62			
Chung et al, 2014 (23)	Depression	3846	678	OR= 1.376 (1.258-1.504)	OR= 1.178 (1.07-1.297)	Age, sex, smoking, alcohol, education, income, physical activity, number of chronic diseases, presence of major cancer
Diaz et al, 2017 (73)	Depression			OR (minor)= 2.38 (1.78-3.19) OR (major)= 2.81 (1.92-4.11)	OR (minor)= 1.95 (1.39-2.74) OR (major)= 2.28 (1.45-3.57)	Effects of age, sex, race and ethnicity, education, body mass index, and poverty
Berg et al, 2012 (45)		121,392	15511		OR= 1.53 (1.5-1.56)	Age and gender

Meurs et al, 2016 (42)	Depression	1811	90		OR= 1.39 (1.1-1.76)	Age, sex, added comorbidity and anxiety disorders
Mantyselka et al, 2011 (74)	Depression				OR (>10)= 1.35 (0.84-2.15) OR (>16)= 1.56 (0.65-3.5)	Demographic, lifestyle, and biological factors
Clarke et al, 2016 (43)	Depression	913	130			
Bouwman et al, 2010 (75)	Depression	181	38	OR= 1.86 (1.27-2.72)	OR= 1.77 (1.13-2.78)	Age, education, family history of diabetes, triglycerides, HDL cholesterol, total Cholesterol, hypertension, smoking and waist circumference
Li et al, 2016 (76)	Depression	529	40		OR= 1.7 (1.25-2.31)	Age, sex, and race, education level, family income, marital status, and family history of diabetes body mass index, diet score, sleep duration, current smoking, drinking status, and physical activity history of chronic disease, and any medication
Seglam et al, 2010 (77)	Depression	500	169			
Kim et al, 2015 (78)	Depression	175	41	OR= 2.24 (1.43-3.51)	OR= 1.65 (0.93-2.92)	Age, education, race/ethnicity, marital status, ratio of family income to poverty, physical activity, BMI, and waist circumference were controlled.

Islam et al, 2015 (79)	Depression	591	100		OR= 6.4 (3.4-12.3)	Education, age occupation, marital status, BMI, HTN, no of complications
Wiltink et al, 2014 (80)	Depression	1074	107			
Bessel et al, 2016 (44)	Depression	1096	63		(Prevalence ratio) PR= 1.31 (0.97-1.78)	Sex, age, race, marital status and smoking, physical activity, body mass index and waist-hip ratio.
Adriaanse et al, 2008 (81)	Depression	126	22	OR (male)= 2.04 (0.76- 5.49) OR (female) = 3.18 (1.31-7.74)	OR (male)= 1.52 (0.47- 4.94) OR (female) = 2.76 (1.01-7.5)	Age, low education and diabetes symptoms (hyperglycemic, cardiovascular, neuropathic pain, sensibility and ophthalmological)
Westra et al, 2016 (82)	Depression			OR= 3.04 (1.57-5.88)	OR= 1.98 (0.95- 4.12)	Age, total body fat percentage, physical activity, education level, time of blood/CES-D collection, serum 25-hydroxyvitamin D, sex
Lee et al, 2014 (25)	Depression	811	152			
Ceretta et al, 2012 (24)	Depression	996	664	OR= 6.5 (5.4-7.5)	OR= 1.8 (1.7-2)	

Table 2.3: Characteristics of selected suicidality studies

Author & Year	Country	Study Design	Setting	Patients N	Age	Female %	Type of Diabetes	Outcome reported	Evaluation of Outcome
Singhal et al, 2014 (83)	England	Retrospective Cohort	Hospital day cases or inpatients	2230207 diabetic patient	≥10	--	Not specified (Hospital records)	Self Harm & Suicide	Record linkage/ICD-10
Webb et al, 2012 (52)	UK	Nested Case Control	General practice research database	48426	17-87	45.4	Not specified (ICD-9)	Self Harm	ICD-9
Myers et al, 2013 (84)	USA	Cross Sectional	Outpatients	145	18-75	59.3	Type 2 (self- reported)	Suicide attempt	Self- reported
Radobuljac et al, 2009 (17)	Slovenia	Cross Sectional		625	14-19	59	Type 1 (record data)	Suicide attempt	Self- reported
Lee et al, 2014 (25)	Korea	Cross Sectional	KNHANES data V	8322	≥40	--	Not specified (self- reported physician diagnosis)	Suicidal ideation	Self reported
Chung et al, 2014 (23)	Korea	Cross Sectional	KNHANES data IV, V	34056	≥20	57	Not specified (self- reported physician diagnosis)	Suicidal ideation & attempt	CIDI-SF
Han et al, 2013 (15)	Korea	Cross Sectional	KNHANES data IV	17065	≥20	57.6	Not specified (self- reported physician diagnosis)	Suicidal ideation	Self-reported
Igwe et al, 2013 (85)	Nigeria	Cross Sectional	Outpatient endocrinology clinic	270	18-64 mean: 51+/- 10.1	64.3	Type 1 & Type 2 at least one year after diagnosis (consultant diagnosis)	Suicidal ideation & attempt	MINI
Handley et al, 2016 (86)	Australia	Cross Sectional	Diabetes MILES national survey	3338	18-70 Mean: 51.7 (13.8)	53.8	Type 1 & Type 2 (the National Diabetes Services Scheme Register)	Suicidal ideation	PHQ-9 (item 9)
Ceretta et al, 2012 (24)	Brazil	Cross Sectional	Outpatients public health facility	994 cases and 2145 control	>18	56.6-59.2	Type 2 (self-reported)	Suicidal ideation	MINI
Sendela et al, 2015 (46)	Poland	Cross Sectional	Outpatients	477	7-18 Mean: 13.1+/-2.7	51.3	Type 1	Suicidal ideation	CDI (Item 9)

Fuller and Sawyer, 2009 (87)	Canada	Cross Sectional	CCHS population survey	82675	≥12	--	Type 1 (self-reported diagnosis and Insulin within one month of diagnosis)	Suicidal ideation	Self- reported
Batty et al, 2012 (50)	Korea	Prospective Cohort	Cancer prevention study participants	1,234,927	30-95	--	Not specified (self report physician diagnosis or medication, study detected diabetes if FBG ≥126 with no history of diabetes)	Suicide	Death Certificates
Yamauchi et al, 2016 (51)	Japan	Prospective Cohort		105,408	51.2+/-7.9	--	Not specified (self report of physician diagnosis or medication usage)	Suicide	Death Certificates/ICD-10
Webb et al, 2014 (48)	Sweden	Cohort	Data records	252,191 cases and 1,260,214 controls	Median 69.3 IQR= (59.2-78.7)	44.5	Type 1 & Type 2 (diabetes register)	Suicide	Death Register
Davis et al, 2015 (49)	Australia	Cohort	Fremantle diabetes study	1413+5660	18- 89.7 Mean: 62.3 ± 12.7	50.2	Not specified	Suicide	Death Certificate or coroner's determination
Webb et al, 2012 (47)		Nested Case Control	Primary care longitudinal database	473 cases 17,460 controls	17-87 Median: 38	--	Not specified (ICD-9)	Suicide	ICD-10/ data linkage

Table 2.4: Data from selected suicidality studies for systematic review and meta-analysis (suicidality studies)

Author & Year	Outcome	Total number of diabetic patients	Number of diabetic events	Reported estimate (95% CI)	Adjusted estimate (95% CI)	Adjustments
Singhal et al, 2014 (83)	S A	2230207	12433	RR=1.6 (1.5-1.6)	--	--
	Suicide	2230207	626	RR= 1 (0.9- 1.1)	--	--
Webb et al, 2012 (52)	Self Harm		81	OR= 1.62 (1.28- 2.06)	OR= 1.28 (1- 1.64)	Clinical depression
Myers et al, 2013 (84)	S A	145	14	--	--	--
Radobuljac et al, 2009 (17)	S A	126	11	--	--	--
	Self Harm	126	16	--	-	--
	S I	126	45	--	--	--
Lee et al, 2014 (25)	SI	811	187		OR= 1.24 (0.95-1.61)	Age, sex, marital status, educational level, co-morbidities, depressive symptoms, stress
Chung et al, 2014 (23)	S A	3846	49	OR=1.562 (1.48-2.13)	OR= 1.413 (1.02- 1.96)	Age, sex, smoking, alcohol, education, income, physical activity, number of chronic diseases and presence of major cancer
	S I	3846	796	OR=1.481 (1.36- 1.61)	1.15 (1.05- 1.26)	Age, sex, smoking, alcohol, education, income, physical activity, number of chronic diseases and presence of major cancer
Han et al, 2013 (15)	SI	1110	206		OR= 1.24 (1.02-1.51)	Age, sex, body mass index, household income, educational level, marital status, smoking, alcohol, and other chronic
Igwe et al, 2013 (85)	SI	270	17			
Handley et al, 2016 (86)	SI	3338	477			
Ceretta et al, 2012 (24)	SI	996	131	OR= 7.1 (5-10)	OR= 2 (1.6-2.3)	
Sendela et al, 2015 (46)	SI	477	47			
Fuller and Sawyer, 2009 (87)	SI	190	31		OR=1.61 (1.08-2.42)	Age and sex

Batty et al, 2012 (50)	Suicide	13452	12		HR (male) = 2.55 (1.3-5), HR (female) = 3.64 (1.12-11.86)	Exercise, smoking status, alcohol consumption, body mass index, height, blood pressure and blood cholesterol.
Yamauchi et al, 2016 (51)	Suicide	4898	41		Or (male)= 1.2 (0.9-1.8) OR (female)= 1.5 (0.7-3)	Age at study entry, public health center area, smoking status, alcohol-drinking habits, body mass index cohabitation, employment status, hours of sleep, frequency of physical exercise, stress level and history of major physical illnesses
Webb et al, 2014 (48)	Suicide	252191	482		RR=3.36 (2.99-3.79)	Age, sex and country of birth
Davis et al, 2015 (49)	Suicide	1413	4		OR= 1.16 (0.38-3.51)	Age and sex
Webb et al, 2012 (47)	Suicide	892	47	OR= 1.18 (0.85-1.62)	OR=0.9 (0.65-1.26)	Sex and age by the case-control matching with added adjustment for clinical depression.

Table 2.5: Meta-regression for depression cohort studies

	Reference Group	Category	Coefficient	95% CI		P-value	R^2
				Lower	Upper		
Depression Evaluation	Depressive Symptoms	Anti-depressants	-0.026	-0.283	0.230	0.218	0.34
		Disorders	0.126	-0.111	0.363		
Level of Adjustment*	No	Full (>5)	0. 299	-0.126	0.726	0.386	0.1
		Partial (<5)	0.024	-0.162	0.212		
Female Percent			0.023	-0.002	0.048	0.07	0
Diabetes	Prevalent Diabetes	Incident Diabetes	-0.014	-0.191	0.162	0.874	0.18
Geographical location	North America	Asia	0.083	-0.155	0.032	0.111	0.36
		Scandinavian	-0.137	-0.375	0.101		
		Europe	-0.147	-0.403	0.108		

R^2 reflects the amount of variability in I^2 that is explained by the model.
* Adjusted for < 5 confounding factors was considered partial, > 5 was considered full

Table 2.6: Results for subgroup analysis for suicide and suicidal ideations

Subgroup	N	Odds ratio	95% CI		P-value for group	P-value for between groups	P-value for heterogeneity	I^2
			Lower	Upper				
Completed suicide								
Sex *(unadjusted)*						**0.552**		
Male	2	1.536	0.78	3.027	0.215		0.068	69.96
Female	2	2.097	0.971	4.528	0.059		0.232	29.89
Sex *(adjusted)*						**0.696**		
Male	2	1.651	0.796	3.427	0.178		0.51	73.71
Female	2	2.059	0.895	4.733	0.089		0.21	36.34
Suicidal ideation								
Type of diabetes						**0.211**		
Type 1	2	1.306	0.637	2.678	0.464		0.01	84.75
Type 2 & not specified	4	2.212	1.473	3.32	<0.001		0.032	70.82
Risk of bias						**0.35**		
Low	2	3.435	0.849	13.898	0.084		<0.001	98.06
Moderate/high	4	1.371	1.005	1.872	0.047		0.032	70.83

Figure 2.1: PRISMA flow chart for study selection process

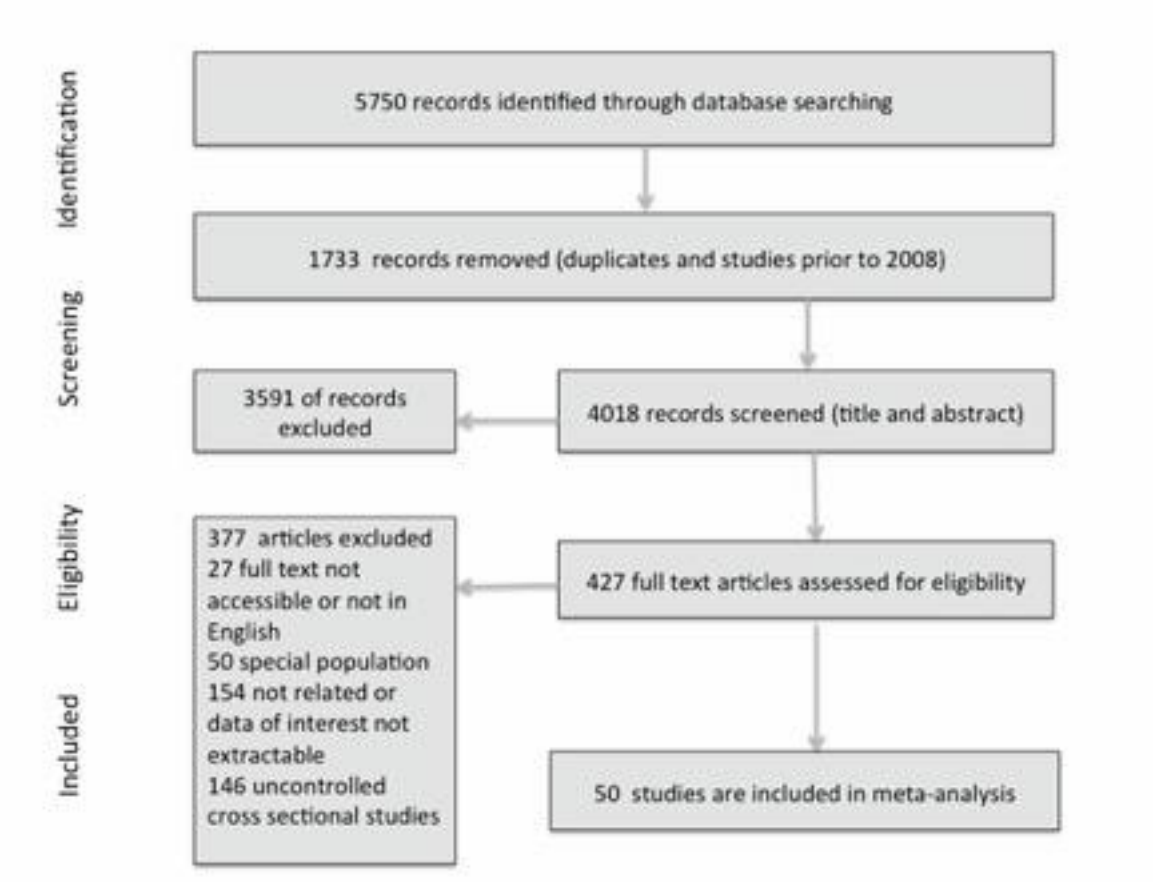
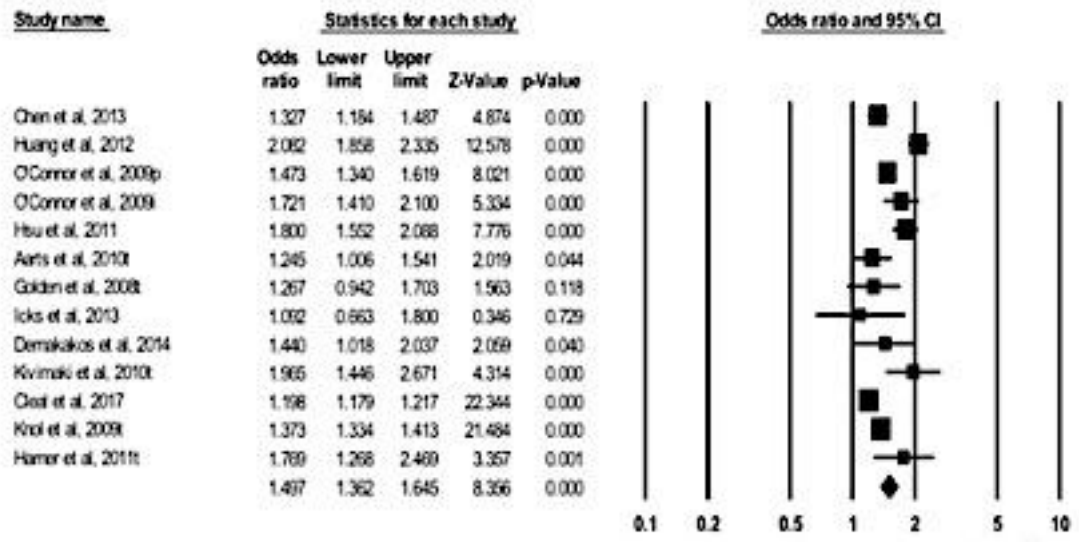
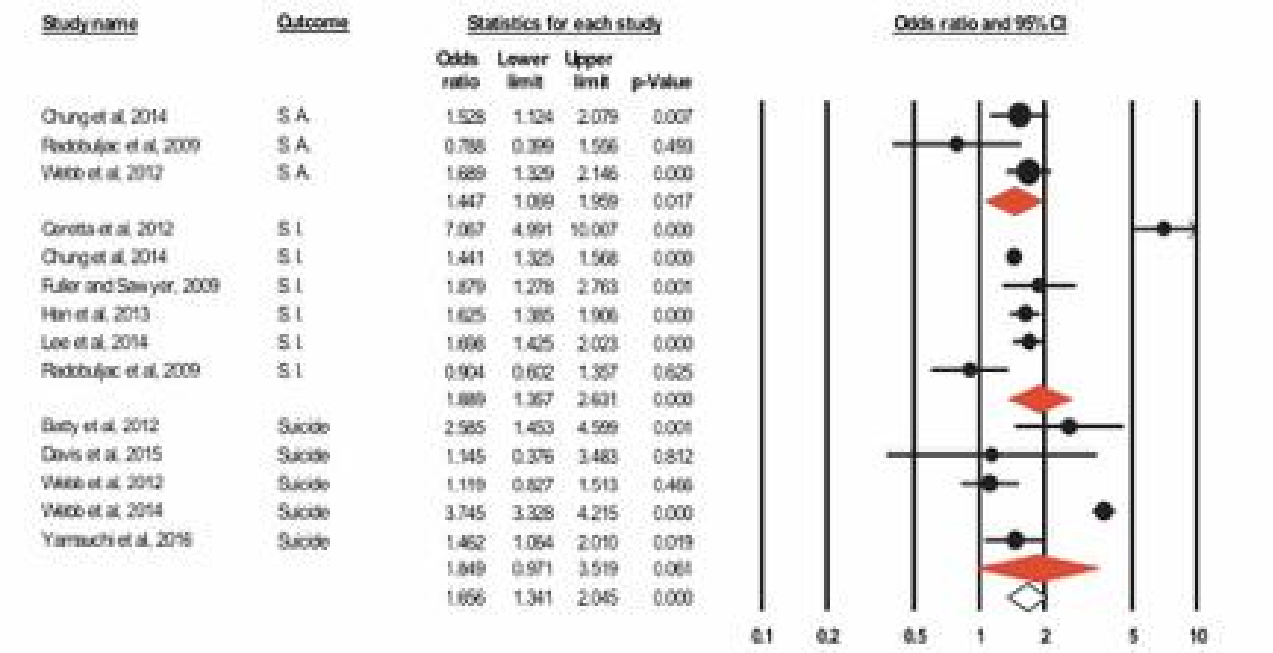


Figure 2.2: Forest plot for the odds ratio of the association between depression and diabetes from cohort studies



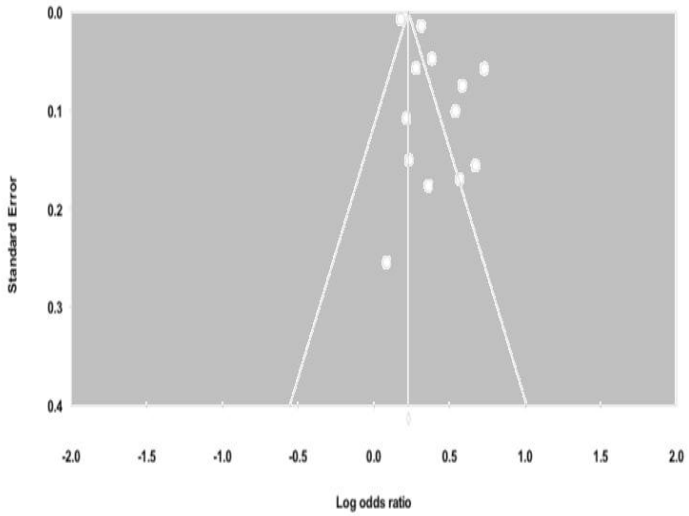
Estimates are in the center of the box and lines represent 95% confidence intervals. Diamond shows the pooled odds ratio size and its 95% confidence interval.

Figure 2.3: Forest plot of unadjusted odds ratio for suicidality and diabetes



SA: suicidal attempts, SI: suicidal ideation. Red diamonds represent pooled odds ratio for each outcome, while white diamond represent the overall odds ratio for the three outcomes.

Figure 2.4: Funnel plots of the met-analysis of published studies.



Each point represents the log odds ratio and the standard error for a single study. The triangle represents the region where 95% of the data points would lie in the absence of a publication bias. The vertical line represents the average log odds ratio found in the meta-analysis.

CHAPTER 3 - EXAMINING THE ASSOCIATION BETWEEN DIABETES, DEPRESSIVE SYMPTOMS, AND SUICIDAL IDEATION AMONG INDIGENOUS CANADIAN PEOPLES LIVING OFF-RESERVE: A CROSS-SECTIONAL, POPULATION BASED STUDY

3.1 Abstract

Background and rationale: Diabetes is a prevalent chronic condition that has been linked to depression and suicidal behavior. The Indigenous peoples of Canada are known to suffer from significant health disparities and higher burden of physical and mental illnesses. The purpose of this study is to examine the association between diabetes, depression, and lifetime suicidal ideation among Indigenous Canadian peoples living off-reserve.

Methods: Data were obtained from the Aboriginal Peoples Survey (APS), 2012. APS is a national, cross-sectional survey of First Nations people living off-reserve, Métis and Inuit living in Canada. A secondary analysis was conducted on a weighted sample of participants to assess diabetes, depression and suicidal ideation. Descriptive statistics and multivariate logistic regression analysis were conducted.

Results: Our study found that the prevalence of depressive symptoms was higher among diabetics (15.67%) compared to non-diabetics (9.27%) (OR 1.82, 95% CI: 1.36- 2.44). After adjusting for socio-demographic variables (aOR=1.64), smoking/alcohol use/drug use (aOR=1.53), anxiety disorders and other chronic illnesses (aOR=1.52), diabetes was still significantly associated with depressive symptoms (p-value= 0.0168). Additionally, diabetics (23.86%) were more likely to report suicidal ideation compared to non-diabetics (18.71%) (OR 1.36, 95% CI: 1.05-1.77). Controlling for the effect of socio-demographics and health related behaviors, diabetes was still associated with a higher risk (aOR=1.40) of reporting suicidal ideation (p-value=0.0231).

Conclusions: Our results suggest that the Indigenous Canadian diabetic patients living off-reserve are at higher risk for depressive symptoms and suicidal ideation. Culturally appropriate co-screening strategies need to be implemented in primary healthcare settings to provide the supports necessary for this vulnerable population. Further research is needed to fully elucidate the nature of these associations in order to develop effective intervention and treatment approaches.

Keywords: Indigenous, Canada, Diabetes, Depression, Depressive symptoms, Suicidal ideation

3.2 Introduction

Indigenous peoples constitute diverse groups of the original inhabitants of Canada and their descendants. According to the Canadian constitution, three major groups are recognized: First Nations, Inuit, and Métis (1). In 2016, there were approximately 1.7 million Indigenous peoples, representing 4.9% of the Canadian population. They represent one of the youngest and fastest growing sub-segments of the Canadian population (2). The Indigenous Canadian peoples have consistently shown high rates of diabetes, depression and suicidal behavior (3, 4, 5). In general, diabetes has been linked to both depression and suicidal behavior (6, 7). However, research that specifically examines these associations among Indigenous Canadian peoples is lacking.

The Indigenous Canadian peoples endure significant health disparities that lead to a higher burden of diseases compared to their non-Indigenous counterparts (8, 9). These health disparities are a by-product of socio-economic, cultural and political factors that negatively impact Indigenous peoples. The socio-economic disadvantages stem from lower levels of education and income, higher unemployment rates, and poor housing conditions (9). The political inequities emerged as a consequence of colonization and resulted in the undermining of indigenous cultures and values, marginalization and social exclusion (10). For instance, the historical trauma caused by the Canadian government's use of residential schools had a wide impact and serious ramifications on Indigenous survivors and their descendants (10), which included: poorer general and self-rated health, high rates of chronic illnesses, addictive behaviors, depression, and suicidal behavior (11). The persistence and growth of these inequities ultimately resulted in health disparities including poor physical and mental health among Indigenous peoples.

Indigenous peoples are particularly vulnerable and disproportionally affected by diabetes in Canada (12). Diabetes, once considered rare among Indigenous communities, is now reported at higher rates among First Nations living off-reserve (10.3%) and among Métis (7.3%) compared to the general Canadian population (5%), and the gap is increasing (13). Even among Inuit people, who historically have reported very low rates of diabetes, the trends are changing as their rates

are becoming comparable to the general population (4.3%). These findings are mainly due to poor dietary choices, limited physical activity, and increased obesity (14, 15). Indigenous individuals are more likely to be diagnosed with diabetes at a younger age, suffer from serious complications and experience worse treatment outcomes compared to non-Indigenous (16). Moreover, under-reporting of the disease and limited access to healthcare services continues to be a growing concern for the Canadian Indigenous peoples (17), suggesting the magnitude of the diabetic epidemic may be larger than estimated (18).

Depression is a common co-morbidity with diabetes (6, 19, 20). Diabetic depressed patients are less likely to adhere to medical treatment and lifestyle changes, resulting in poor prognosis for both conditions (21). This co-morbidity has been widely examined in different populations but there is scarcity of research among Indigenous peoples. In Canada, a study that assessed health related quality of life found that Indigenous participants reported lower scores than non-Indigenous and diabetes was more prevalent among Indigenous participants (22). It is known that Indigenous peoples of Australia face health disparities that are similar to the Indigenous peoples of Canada (23). A study in Australia evaluated the prevalence of depression among urban diabetic patients and found it to be two times greater among the Indigenous compared to the non-Indigenous population (24). The authors further reported that among Indigenous individuals, depression tended to be more severe in nature and in many cases, undiagnosed and left untreated (24).

Indigenous Canadian populations have one of the highest rates of suicide worldwide (25)**.** Among the First Nations, suicide rates are two times the national average and alarmingly, the Inuit suicide rates are among the highest in the world (6 to 11 times the national average) (4). Suicidal ideation is a crucial component of suicidal behavior, which often precedes suicidal attempts or completed suicide, and is known to be a strong predictor for suicidal death (26). In 2012, 24% of First Nations living off-reserve, 23.5% of Inuit, and 19.6% of Métis people reported lifetime suicidal ideation compared to 11.1% in the general Canadian population (27). Similar to depression, suicidal behavior has been linked to diabetes. However, the scientific evidence is limited and at times, contradictory (7, 28) and therefore, more research is needed in this area.

Despite Indigenous peoples in Canada consistently reporting higher prevalence of diabetes, depression and suicidality, to the best of our knowledge, no studies explored the associations between these conditions among this vulnerable population. Therefore, the aim of the present study was to use data from the Aboriginal Peoples Survey (APS), 2012 to: (1) determine the prevalence of depressive symptoms and suicidal ideation among patients with diabetes; (2) investigate whether diabetes is associated with a higher risk of depression and suicidal ideation; and (3) assess whether these associations vary by different characteristics among the Indigenous Canadian populations living off-reserve.

3.3 Methods

3.3.1 Study characteristics

Design: Cross-sectional population based observational study.

Participants: The Indian reserve system is governed by the Indian Act (1876) and relates to the First Nations people of Canada. Historically, First Nations people were legally bound by the Canadian government to live on reserve. The ban was lifted in 1951 and First Nations were allowed to live on or off-reserve (29). Presently, the majority (62%) of the First Nations population live off-reserve, while the remaining portion (38%) live on-reserve (30). Métis and Inuit people traditionally do not live on reserves. In this study, we are examining the off-reserve Indigenous population (First Nations, Métis and Inuit) ages 15 years old or older.

Data source*:* The present study used data from the Aboriginal People Survey (APS) conducted by Statistics Canada in 2012. It is a national survey on the social and economic conditions of First Nations living off-reserve, Métis and Inuit. The APS had a participation rate of 76% and used stratification-specific domains for sampling (31). To ensure that statistical estimates would be representative of the Indigenous Canadian population, sampling weights computed by Statistics Canada were incorporated into the analysis and the Taylor linearization method was used to estimate the covariance matrix of the regression coefficients (SURVEYLOGISTIC procedure in SAS).

3.3.2 Measures

***Measuring tool*:** Evaluation of depressive symptoms in this study was based on a modified version of the K-10 distress scale. The K-10 scale is used to evaluate the distress experienced by individuals during the past 30-days (32). The K-10 scale and a number of its modified versions (K-5, K-6) have been previously used among Indigenous peoples (33, 34). While these tools measure distress rather than depression or anxiety, their scores correlate well with depression and anxiety (32). Self-reported suicidal ideation was part of the APS questionnaire.

Outcome measures

The main outcome measures for this study were depressive symptoms and lifetime suicidal ideation.

Depressive symptoms: The present study used a modified version of the K-10 scale to assess depressive symptoms among Indigenous participants. Six questions were selected and addressed components of two domains that included: core symptoms (depressed mood and reduced energy) and associated symptoms (unworthiness and hopelessness) (35). These questions were: "In the past 4 weeks, about how often did you feel: (a) tired out for no good reason, (b) hopeless, (c) depressed, (d) everything was an effort, (e) sad that nothing could cheer you up, and (f) worthless?" Responses were ranked on a Likert scale: (a) all of the time, (b) most of the time, (c) some of the time, (d) a little of the time, and (e) none of the time. To assess the reliability of these questions, Cronbach's α was calculated, and found to be satisfactory (0.837). A mean score for each respondent was calculated and adjusted for the number of questions answered. Participants were dichotomized on the basis of a recommended cut-off value from the K-10 scale (32). Those who scored 2.5 or greater were considered "depressed" while those with scores less than 2.5 were "not depressed."

Suicidal ideation: Lifetime suicidal ideation was assessed by asking the following question: "Have you ever seriously considered committing suicide or taking your own life?" The answer was either "yes" or "no".

Exposure variable

The main exposure variable was self-reported diabetes status. Diabetics were those respondents, who answered "yes" to the following question: "We are interested in conditions diagnosed by a health professional and that are expected to last or have already lasted 6-months or more. Do you have diabetes?"

Control variables (covariates)

In the present study, socio-demographic, health related behavior, and clinical profile variables were used as controls in our logistic regression models. Selection of these variables was based on the recommendations made in the existing scientific literature (36).

***Socio-demographic variables*:** These included, age (≤ 19, 20-34, 35-54, ≥ 55 years old), sex (male or female), marital status (single, married, widowed/separated/divorced, living in common-law), Aboriginal identity (First Nations, Métis, Inuit), highest level of education attained [(a) grade 8 or lower/some secondary education; (b) secondary school diploma/some postsecondary education; (c) postsecondary certificate or diploma below bachelor level; (d) bachelor's degree/ university certificate or diploma or degree above bachelor level].

Health related behavior variables: These included, smoking status (daily, occasional, non-smoker), alcohol use (regular, occasional, non-drinker) and drug-use (yes, no).

Clinical profile variables: These included, chronic illnesses [a derived variable that combined responders who answered "yes" to one of the following questions: ("Do you have asthma, fibromyalgia, learning disability, attention deficit disorder, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), intestinal or stomach ulcers, bowel disorder, hypertension, heart disease and other physical or mental disorders")] and anxiety disorders [assessed using the following question: "Do you have an anxiety disorder such as a phobia, obsessive-compulsive disorder or a panic disorder?" (yes, no)]. Additionally, for suicidal ideation, mood disorders were included [as a covariate based on the question: "Do you have a mood disorder such as depression, bipolar disorder, mania or dysthymia?" (yes, no)].

3.3.3 Statistical analysis

Initially, cross tabulations were performed examining the distribution of observations by depressive symptoms, and suicidal ideation status for each variable. Due to data confidentiality concerns, results are reported as rounded weighted frequencies. The unadjusted association between diabetes and other covariates on depressive symptoms and suicidal ideation were calculated using univariate binary logistic regression models. Covariates with p-value < 0.25, qualified to be included in the multivariable logistic regression models.

For each outcome, four logistic regression models were constructed: Model 1 (crude unadjusted associations between exposure and outcome variable), Model 2 (adjusts for the effect of socio-demographic confounders), Model 3 (additionally adjusts for health related behavior), and Model 4 (additionally adjusts for clinical profile variables). If the p-value for a covariate was less than 0.05, the variable was retained in the multivariable model. Age and gender were considered important confounders, and therefore, adjusted in the model irrespective of their p-values. The Akaike Information Criterion (AIC) comparisons were used to compare the models (lower is better).

Confounders and interaction assessment

To assess whether a covariate had a confounding effect, a change of 20% or more in the coefficient of the main exposure variable (diabetes) was used as a cut-off (37). Effect modifications were investigated by examining all possible two-way interactions for the main exposure variable (diabetes) with predictors and confounders included in the main effect model. Interactions were assessed based on their p-value and (AIC) comparisons.

Model diagnostics

The variance inflation factor (VIF) and tolerance for all variables were calculated to assess whether multicollinearity (if present) would significantly affect reported estimates. We used a cut-off at 2.5 for VIF and 0.4 for tolerance. For model predictability, the receiver operating characteristic (ROC) curve was generated and the area under the curve (AUC) was measured and reported. All statistical analyses were performed using SAS V.9.4 (SAS Institute Inc., Cary, NC, USA).

3.4 Results

3.4.1 Depressive symptoms

The weighted total number of Indigenous participants who responded to the depression questions was 963,110.The total mean score per participant ranged from 1 to 5 (1= least depressive symptoms). The overall distribution of the mean score was right skewed as more participants reported relatively low levels of depressive symptoms (median= 1.33). Of the participants, 8.34% (n=80,350) were classified as having depressive symptoms. The prevalence of depressive symptoms among those who reported a physician diagnosis of diabetes was 15.67% (n= 11,100), compared to 9.27% (n= 69,070) among the non-diabetic participants. Table 3.1 depicts the characteristics of the study participants, stratified by their depressive symptoms status.

1.1 Univariate analysis

Model 1: Diabetics were more likely to report depressive symptoms (OR= 1.82, 95% CI: 1.36-2.44, p-value <0.0001) compared to non-diabetics. Additional crude estimates considering socio-demographic variables showed that being female, middle aged, not married, lower levels of education and First Nations was associated with significantly higher odds of reporting depressive symptoms. Health related behavior variables showed that regular smokers, occasional alcohol drinkers, and drug users had higher odds of depressive symptoms. Clinical profile variables showed that having chronic illnesses other than diabetes and being diagnosed with an anxiety disorder were the strongest predictors of depressive symptoms in our analysis. All variables had a p-value < 0.25 in the univariate analysis. Table 3.2 lists the crude odds ratios and 95% confidence intervals for the different covariates of depressive symptoms.

1.2 Multivariate analysis

Model 2: Our results indicated that the association between diabetes and depressive symptoms remained significant after adjusting for socio-demographic variables (aOR=1.64, 95% CI: 1.17-2.31, p-value=0.0043). There was no significant effect for Indigenous identity (p-value =0.1682) and therefore, this variable was not included in model 3.

Model 3: After adjusting for both socio-demographics and health related behaviors, diabetes remained significantly associated with depressive symptoms (aOR=1.53, 95% CI: 1.12- 2.08, p-value=0.0073). Interestingly, regular alcohol use had a significant protective effect against depressive symptoms (p-value <0.0001). The odds of depressive symptoms for Indigenous participants who reported regular use of alcohol were 44% lower than the odds of non-users (aOR= 0.56, 95% CI, 0.44 – 0.71, p-value < 0.0001). Level of education was not a significant predictor (p-value= 0.1094) and therefore, it was not included in model 4.

Model 4: Our results remained significant after further adjusting for clinical profile variables. The odds of having depressive symptoms for patients with diabetes were 52% higher than those reported for non-diabetics (aOR=1.52, 95% CI: 1.08-2.14, p-value=0.0168). Socio-demographic variables showed that the odds for females were 1.5 times greater than those for males (aOR=1.5, 95% CI: 1.22-1.85, p-value =0.0001). Married participants had lower risk of reporting depressive symptoms compared to single and divorced/separated/widowed individuals but not significantly different from participants living in common-law relationships. Health related behaviors showed that the odds of depression among daily smokers were 1.83 times greater than those of non-smokers (aOR=1.83, 95% CI: 1.48-2.26, p-value <0.0001) but not different from those seen in occasional smokers. Participants who reported use of drugs had 1.58 times greater odds of depressive symptoms relative to non-users (aOR= 1.58, 95% CI: 1.23-2.03, p-value= 0.0003). Focusing on clinical profile, being diagnosed with anxiety disorders was the strongest predictor of depression (aOR= 4.16, 95% CI: 3.32- 5.22, p <0.0001). Respondents who reported having other chronic illnesses were at higher risk of having depressive symptoms (aOR= 2.73, 95% CI: 2.15- 3.48, p-value <0.0001). Results of the multivariable analysis are shown in Table 3.3.

3.4.2 Suicidal ideation

The weighted total number of Indigenous participants who responded to the suicidal ideation questions was 694,960. The overall prevalence of suicidal ideation was 19.08% (n=132,570). The prevalence of suicidal ideation among diabetics was 23.86% compared to 18.71% among the non-diabetic respondents. Table 3.4 depicts the characteristics of the study participants, stratified by their suicidal ideation status.

2.1 Univariate analysis

Model 1: Diabetics were more likely to report suicidal ideation (OR= 1.36, 95% CI: 1.05-1.77, p-value =0.0193) compared to non-diabetics. Additional crude estimates considering socio-demographic variables showed that being female, middle aged, unmarried and First Nations or Inuit had significantly higher odds of reporting suicidal ideation. Health related behavior variables showed smokers, non-alcohol users, and drug users had higher odds of suicidal ideation. Clinical profile variables showed that chronic illnesses and mental disorders (anxiety and mood) were the strongest predictors of suicidal ideation. Interestingly, the dichotomized depression score (based on the modified K-10 scale) was strongly related to suicidal ideation; the odds of experiencing lifetime suicidal ideation for those who were classified as having depressive symptoms were 8.27 times higher than those who did not (95% CI: 6.8 - 10.05, p-value <0.0001). Table 3.2 lists the crude odds ratios and 95% confidence intervals for the different covariates of suicidal ideation.

2.2 Multivariate analysis

Model 2: After adjusting for socio-demographic variables, the association between diabetes and suicidal ideation remained significant (aOR=1.44, 95% CI: 1.09-1.92, p-value=0.0117). Level of education was not a significant predictor of suicidal ideation (p-value=0.1104) and therefore, it was not considered in Model 3.

Model 3: The strength of association between diabetes and suicidal ideation was maintained after adjusting for both socio-demographics and health related behavior variables (aOR=1.40, 95% CI: 1.05-1.88, p-value =0.0231). Once again, regular alcohol users were 41% less likely (OR= 0.59, 95% CI: 0.49- 0.72, p-value <0.0001) to self-report suicidal ideation compared to non-users. In this model, Indigenous identity was not a significant predictor of suicidal ideation (p-value= 0.1856) and therefore, it was not included in Model 4.

Model 4: Our results found that the risk of suicidal ideation among diabetics was no longer significant after additionally controlling for the effects of health related variables (aOR = 1.17, 95% CI: 0.87–1.56, p -value = 0.3012). Socio-demographic variables showed that individuals aged between 35 and 54 years old had significantly higher risk of reporting suicidal ideation

compared to individuals 55 years old or older (aOR= 1.23, 95% CI: 1.01- 1.64, p-value= 0.0385). Consistent with our depression findings, being male, married or living in common-law relationship was associated with significant lower risk of reporting suicidal ideation. Health related behaviors showed that drug users (aOR= 2.82, 95% CI: 2.33- 3.42, p-value< 0.0001) and daily smokers (aOR= 1.39, 95% CI: 1.17- 1.64, p-value= 0.0001) are at higher risk of suicidal ideation, while regular alcohol use maintained its protective effect. Clinical profile variables showed that mood disorders were the strongest predictor of suicidal ideation (aOR= 4.64, 95% CI: 3.77-5.72). Participants diagnosed with anxiety disorders (aOR= 1.52, 95% CI: 1.22- 1.88) or other chronic illnesses (aOR= 1.73, 95% CI: 1.44- 2.07) were more likely to report suicidal ideation compared to those who were not. Table 3.6 illustrates results of the multivariable analysis with suicidal ideation as the outcome of interest.

3.5 Discussion

In the present study, we examined the association between diabetes, depression, and lifetime suicidal ideation in a national sample of the Indigenous Canadian peoples living off-reserve. Our data show that Indigenous diabetics are at a significantly higher risk for experiencing depressive symptoms compared to their non-diabetic counterparts. That effect maintained its strength after adjusting for socio-demographics, health related behaviors and clinical profile factors. Furthermore, our results indicated that diabetes was associated with a higher risk for suicidal ideation, when considering socio-demographic and health related behavioral factors.

The crude prevalence of depressive symptoms among Indigenous diabetic participants was 15.67% compared to 9.27% among non-diabetics. Our study findings corroborate those reported by Davis et al., who examined depression among Indigenous Type 2 diabetic patients in Australia. They found prevalence rates to be higher than those reported among the general Australian population (24). However, other studies contradict our findings. One of these studies assessed depression (and other factors) among Canadian Indigenous participants with impaired glucose tolerance and Type 2 diabetes. They found no difference in the prevalence between the diabetic and pre-diabetic group compared to the normo-glycemic group. Yet, this study suffered from a number of limitations including a high risk of selection bias and limited study power (38).

The high prevalence of depression observed in our study is concerning, especially when one considers the findings reported in the literature that help highlight the lack of attention to depression screening and management among Indigenous diabetic patients in primary healthcare settings (34, 39). Therefore, it is not surprising to note the many negative consequences of untreated depression, especially in the cases of Indigenous diabetics, which may manifest as higher burdens of disability, increased cost of hospitalization and even premature death (40).

Our results show that diabetes was independently associated with higher risk for experiencing depressive symptoms, even after adjusting for all control variables. This finding supports the growing body of literature that suggests that diabetes and depression are related (6, 19, 20, 41, 42). There is evidence of a bidirectional association whereby diabetes increases the risk of depression (6, 19, 20) and depression increases the risk of diabetes (41, 42). Given the exploratory, cross-sectional nature of our study, our results confirm the existence but are unable to determine the directionality of this association.

Among the more plausible explanations for the association between diabetes and depression among the Indigenous Canadian population is the role played by socio-economic status (SES). In general, SES is a strong predictor of both diabetes and depression (43-45). SES plays an important role as diabetes is known to be inversely related to the level of income, education, and housing (46, 47). Within the Canadian Indigenous context, the social, cultural and economic inequities experienced by this population, adversely impact their SES (48). Their continued struggle to meet basic needs with limited resources, disadvantageous conditions and risky behaviors (e.g. smoking, alcohol drinking and drug use) impose high levels of chronic stress (49) that may lead to the development of diabetes, depression and suicidal behavior (50, 51).

In our study, the prevalence of lifetime suicidal ideation among Indigenous diabetics was 23.86% compared to 18.71% in non-diabetic respondents. Controlling for the differences in socio-economic and health related behavioral factors; diabetes was a statistically significant predictor of suicidal ideation, which is in concordance with previous studies (52, 53). This finding may not be surprising as depression is a strong risk factor for suicidal behavior (54) and therefore, it can act as a mediating step in the association between diabetes and suicidal behavior (55).

Nevertheless, when considering the problems of diabetes and suicidal ideation in the Indigenous population of Canada, historical context cannot be ignored. For example, the effect of the traumatic experiences of Indigenous peoples in residential schools has been linked to both suicidal behavior and diabetes (56, 57). It was demonstrated that the structural violence practiced in residential schools not only increased the risk of suicidal behavior among the schools' attendees, but also their descendants by suffering from "intergenerational trauma" (56). Additionally, these institutions suppressed indigenous dietary practices and replaced traditional healthy foods with western foods that are high in salt, sugar and fat (57). These unhealthy dietary practices were maintained in later generations (57) and may have contributed to the epidemic of diabetes in the Indigenous population.

It is interesting to note that, in our results, regular alcohol use was associated with a significant protective effect for depressive symptoms and suicidal ideation. This finding seems to contradict those previously published in the literature. These studies mainly focused on heavy and hazardous use of alcohol and found a positive association with depression and suicidal behavior (58, 59, 60). Other studies have also described a J shaped relationship, whereby regular low-to-moderate drinkers have experienced lower risk of depression relative to abstainers (61, 62). Several explanations for this pattern have been proposed, which include: (a) a direct protective effect of alcohol on depression, similar to its effect on coronary heart disease (63); and (b) social aspects of alcohol use related to drinking behavior, whereby in certain cultures, low-to-moderate regular drinkers may psychologically benefit by becoming better socially adjusted compared to those who never drink alcohol (61). However, our study findings should be interpreted with caution since key details in alcohol use were not available (e.g. frequency, quantity, volume, duration) among our participants, which could significantly change the pattern of the inter-relationship between alcohol use, depression and suicidal behavior (64).

Strengths and limitations

This study has several strengths, which include: (a) a large, representative, national sample, (b) use of weights to statistically adjust our sample, which resulted in the generalizability of our findings among the Indigenous Canadian population living off- reserve; (c) adjusting for a wide variety of factors (socio-demographic, health related behavior, and clinical profile variables); and

(d) participants were not recruited based on their diabetes, depression, or suicidal ideation status, therefore, the potential for selection bias was minimal.

This study also has some limitations: (a) the cross-sectional design is helpful in identifying the associations between diabetes, depression and suicidal ideation, but cannot be used to infer directionality and causality; (b) the use of self-report survey data may be prone to recall bias and social desirability but the validity of the survey has been well established (31); (c) due to the sensitivity of the topics and possible stigmatization, there is a possibility that participants with depression or suicidal ideation either did not participate in the survey or did not accurately respond to particular questions, and (d) according to Statistic Canada, the sample used for the suicidal ideation question may not be representative for those younger than 18 years old and therefore, caution is required in interpreting the findings.

Implications for research and clinical practice

This study provides previously unavailable information about diabetes, depression and suicidal ideation in the Indigenous Canadian population living off-reserve. It underscores the need to improve awareness among diabetic patients and healthcare providers on the common co-occurrence of these conditions. It also highlights the importance of depression and suicidal behavior screening for diabetic patients in primary healthcare settings. Screening and management of depression and suicidal behavior is complicated in Indigenous patients due to cultural differences that can represent a barrier to effective screening. Therefore, when developing and implementing health policies and health promotion initiatives to address depression and suicidal behavior among Indigenous diabetics, focus should be given on culturally sensitive and acceptable strategies.

Further research is needed to understand the potential biological and psychological mechanisms implicated in the association between depression and suicidal behavior in patients with diabetes. Longitudinal studies are required to characterize risk factors, identify the course and effect of co-morbidity and assess how it relates to prognosis and response to treatment. It is essential when conducting research with Indigenous peoples to use an intersectional approach to study the interplay between different social, political and cultural factors. Future research that examines the

patterns of alcohol use among Indigenous diabetic patients and its effect on development of depression and suicidal behavior is required.

3.6 Conclusions

Our study found that the Indigenous Canadian diabetic population living off-reserve is at a higher risk of experiencing depressive symptoms and suicidal ideation compared to non-diabetics. Raising awareness, improving the training of healthcare professionals and developing culturally appropriate co-screening strategies are important steps in reducing the burden of depression and suicidal behavior among Indigenous diabetics. Such co-screening efforts can help in the early identification and management of these complex cases and decrease the burden of further disability, hospitalization and premature death. Future research is required to elucidate the temporal nature of the association between diabetes, depression and suicidal ideation among the Indigenous peoples of Canada.

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Table 3.1: Characteristics of study participants based on depression symptoms

Variable	Categories	Depression*		Total
		Yes N (%)	No N (%)	N (%)
Overall		80350 (8.34)	882760 (91.66)	963110
Diabetes (n= 815630)	Yes	11080 (15.67)	58800 (84.33)	80160 (9.83)
	No	69070 (9.27)	675740 (90.73)	735470 (90.17)
Socio-demographic variables				
Age (n=963110)	≤ 19 years	7290 (2.66)	266430 (97.34)	273720 (28.42)
	20-34 years	23150 (10.26)	202430 (89.74)	225580 (23.42)
	35-54 years	35170 (11.96)	258800 (88.04)	293970 (30.52)
	>55 years	14740 (8.68)	155100 (91.32)	169840 (17.63)
Sex (n=93110)	Male 1	24850 (5.53)	424610 (94.47)	449460 (46.67)
	Female 2	55500 (10.81)	458150 (89.19)	513650 (53.33)
Marital status (n=794750)	Married	17440 (6.56)	248340 (93.44)	265780 (33.44)
	Common- low	11250 (9.95)	101800 (90.05)	113050 (14.22)
	Widowed/separated/ or divorced	17550 (16.39)	89530 (83.61)	107080 (13.47)
	Single	33950 (10.99)	274900 (89.01)	308850 (38.86)
Aboriginal identity (n=963110)	First Nations	44930 (9.09)	448920 (90.9)	493850 (51.28)
	Métis	31630 (7.59)	384650 (92.4)	416280 (43.22)
	Inuit	3800 (7.17)	49190 (92.85)	52980 (5.5)
Level of education (n=709690)	Grade 8 or lower/some secondary education	25340 (14.43)	150270 (85.57)	175610 (24.74)
	Secondary school diploma/some postsecondary education	23300 (10.23)	204430 (89.77)	227730 (32.09)
	Postsecondary certificate or diploma below bachelor level	23030 (9.71)	214190 (90.29)	237220 (0.3343)

	Bachelor's degree/ university certificate or diploma or degree above bachelor level	4040 (5.84)	65100 (94.16)	69140 (9.74)
Health related behavior				
Smoking (n=812530)	Daily	38980 (17.43)	184670 (82.57)	223650 (27.52)
	Occasional	8260 (11.03)	66620 (88.96)	74880 (9.22)
	Non smoker	32970 (6.41)	481040 (93.59)	514010 (63.26)
Alcohol use (n=)	Daily	38380 (9.46)	367340 (90.54)	405710 (50.18)
	Occasional	20840 (12.14)	150860 (87.86)	171690 (21.23)
	Non drinker	20990 (9.08)	210120 (90.92)	231110 (28.58)
Drug use (n=688630)	Yes	61000 (14.27)	366370 (85.73)	427370 (62.06)
	No	19150 (4.48)	242110 (92.67)	261260 (37.94)
Clinical profile				
Chronic illness (n=963110)	Yes	69490 (14.56)	407810 (85.44)	485810 (50.44)
	No	10860 (2.23)	474950 (97.76)	477300 (49.56)
Anxiety disorders (n=814900)	Yes	35850 (34.06)	69410 (65.94)	105260 (12.91)
	No	44210 (6.23)	665430 (93.77)	709640 (87.08)

***** Rounded weighted frequency

Table 3.2: Crude odds ratios (with 95% confidence interval) for depressive symptoms

Variable	Category	Odds ratio	95% CI		P-value
			Lower	Upper	
Socio-demographic variables					
Age (Ref: >55 years)	≤ 19 years	0.29	0.22	0.38	<0.0001
	20-34 years	1.20	0.92	1.58	0.1808
	35-54 years	1.43	1.09	1.87	0.0097
Sex (Ref: Male)	Female	2.07	1.72	2.49	<0.0001
Marital Status (Ref: Married)	Single	1.75	1.68	1.82	<0.0001
	Widowed/separated/ or divorced	2.77	2.71	2.84	<0.0001
	Common law	1.56	1.16	2.08	0.0029
Aboriginal Identity (Ref: Métis)	First Nations	1.22	1.02	1.45	0.0296
	Inuit	0.94	0.88	1.00	0.4359
Level of Education (Ref: Bachelor's degree/ university certificate or diploma or degree above bachelor level)	Grade 8 or lower/some secondary education	2.70	1.89	3.85	0.0007
	Secondary school diploma/some postsecondary education	1.84	1.60	2.77	<0.0001
	Postsecondary certificate or diploma below bachelor level	1.73	1.53	1.92	<0.0001
Health behavior					
Smoking (Ref: Non-smoker)	Daily	3.03	2.56	3.70	<0.0001
	Occasional	1.79	1.63	2.03	0.0003
Alcohol use (Ref: Non-drinker)	Occasional	1.38	1.08	1.77	0.0098
	Regular	1.05	0.84	1.29	0.6828
Drug use (Ref: No)	Yes	2.11	1.71	2.59	<0.0001
Clinical profile					
Chronic illnesses (Ref: No)	Yes	7.45	6.03	9.20	<0.0001
Anxiety disorders (Ref: No)	Yes	7.78	6.41	9.43	<0.0001

Table 3.3: Adjusted odds ratios (with 95% confidence intervals) of depressive symptoms

		Model 1	P-value	Model 2 N=684300	P-value	Model 3 N=638610	P-value	Model 4 N=684010	P-value
Diabetes (Ref: No)	Yes	1.82 (1.36-2.44)	<0.0001	1.64 (1.17-2.31)	0.0043	1.53 (1.12 – 2.08)	0.0073	1.52 (1.08-2.14)	0.0168
Age (Ref: >55 years)	≤ 19 years			0.86 (0.55- 1.35)	0.5188	0.84 (0.53-1.32)	0.4535	1.09 (0.73- 1.65)	0.6564
	20-34 years			1.42 (0.97- 2.08)	0.0729	1.31 (0.93-1.84)	0.1206	1.1 (0.76-1.6)	0.6189
	35-54 years			1.85 (1.33-2.58)	0.0002	1.75 (1.31-2.35)	0.0002	1.2 (0.86-1.67)	0.2828
Sex (Ref: Male)	Female			1.93 (1.59-2.35)	<0.0001	2.03 (1.67-2.47)	<0.0001	1.5 (1.22-1.85)	0.0001
Marital status (Ref: Married)	Common-low			1.56 (1.15- 2.13)	0.0046	0.91 (0.68-1.21)	0.5101	1.29 (0.94-1.79)	0.1132
	Widowed/ separated/ divorced			2.48 (1.82- 3.38)	<0.0001	1.85 (1.41-2.43)	<0.0001	2 (1.45-2.76)	<0.0001
	Single			2.15 (1.63 -2.84)	<0.0001	1.47 (1.14-1.89)	0.0029	1.87 (1.48-2.26)	<0.0001
Aboriginal identity (Ref: Métis)	First Nations			1.148 (1.147-1.149)	<0.0001	-	-	-	-
	Inuit			0.92 (0.69- 1.19)	0.4990	-	-	-	-
Education level (Ref: Bachelor's degree/ university certificate or diploma or degree above bachelor level	Grade 8 or lower/some secondary education			3.29 (2.23- 4.85)	<0.0001	1.48 (1.04-2.11)	0.0309	-	-
	Secondary school diploma/some postsecondary education			2.05 (1.4- 2.99)	0.0002	1.48 (1.06-2.08)	0.223	-	-

	Postsecondary certificate or diploma below bachelor level	1.84 (1.25-2.69)	0.0018	1.29 (0.94-1.79)	0.1156	-	-
Smoking (Ref: Non smoker	Daily	-	-	1.58 (1.29-1.93)	<0.0001	1.83 (1.48-2.26)	<0.0001
	Occasional			0.92 (0.68-1.24)	0.5647	1.28 (0.89-1.85)	0.1877
Alcohol use (Ref: Non drinker)	Regular	-	-	0.56 (0.44-0.71)	<0.0001	0.89 (0.69- 1.14)	0.3485
	Occasional			0.81 (0.62-1.05)	0.1094	0.99 (0.75-1.29)	0.9120
Drug use (Ref: No)	Yes	-	-	2.361 (1.87- 2.98)	<0.0001	1.58 (1.23-2.03)	0.0003
Chronic illnesses (Ref: No)	Yes	-	-	-	-	2.73 (2.15-3.48)	<0.0001
Anxiety disorders (Ref: No)	Yes	-	-	-	-	4.16 (3.32-5.22)	<0.0001
AUC		0.653		0.673		0.768	

Model 1: unadjusted
Model 2: Adjusts for age, sex, marital status, aboriginal identity, and level of education.
Model 3: Adjusts for age, sex, marital status, level of education, smoking, alcohol use, and drug use.
Model 4: Adjusts for age, sex, marital status, smoking, alcohol use, drug use, chronic illnesses, and anxiety disorders.

Table 3.4: Characteristics of study participants based on suicidal ideation status

Variable	Categories	Suicidal ideation*		Total
		Yes N (%)	No N (%)	N (%)
Overall		132570 (19.08)	562390 (80.92)	694960
Diabetes (n=689590)	Yes	15450 (23.86)	49290 (76.14)	64740 (9.39)
	No	116890 (18.71)	507960 (81.29)	624850 (90.61)
Socio-demographic variables				
Age (n=694960)	≤ 19 years	9810 (13.15)	64780 (86.85)	74580 (10.73)
	20-34 years	38930 (19.92)	156440 (80.07)	195360 (28.11)
	35-54 years	61330 (22.63)	209630 (77.37)	270960 (38.98)
	>55 years	22510 (14.61)	131540 (85.38)	154060 (22.17)
Sex (n=694960)	Male 1	48730 (12.53)	257570 (84.09)	306300 (44.07)
	Female 2	83840 (21.57)	304820 (78.43)	388660 (55.92)
Marital status (n=686560)	Married	33800 (13.85)	210260 (86.15)	244060 (35.54)
	Common-law	20060 (19.79)	81310 (80.21)	101360 (14.76)
	Widowed/separated/ or divorced	26650 (26.75)	72980 (73.25)	99630 (14.51)
	Single	51590 (21.36)	189930 (78.64)	241520 (35.18)
Aboriginal identity (n=694960)	First Nations	71780 (20.58)	276970 (79.41)	276970 (50.18)
	Métis	53470 (17.11)	259030 (82.89)	312500 (44.96)
	Inuit	7330 (21.74)	26380 (78.25)	33710 (4.85)
Level of education (n=641090)	Grade 8 or lower/some secondary education	30120 (20.15)	119340 (79.84)	149460 (23.31)
	Secondary school diploma/some postsecondary education	40300 (19.8)	163200 (80.19)	203510 (31.74)

	Postsecondary certificate or diploma below bachelor level	44380 (19.96)	177960 (80.04)	222340 (34.68)
	Bachelor's degree/ university certificate or diploma or degree above bachelor level	10690 (16.25)	55100 (83.75)	65790 (10.26)
Health related behavior				
Smoking (n=689640)	Daily	58160 (27.99)	149620 (72.01)	207770 (30.13)
	Occasional	12980 (19.69)	52930 (80.31)	65900 (9.56)
	Non smoker	61310 (14.73)	354660 (85.26)	415970 (60.32)
Alcohol use (n=688930)	Daily	66040 (17.38)	313860 (82.62)	379900 (55.14)
	Occasional	31850 (20.99)	119840 (79.00)	151690 (22.02))
	Non drinker	34490 (21.92)	122850 (78.08)	157340 (22.83)
Drug use (n=686310)	Yes	108150 (25.36)	318300 (74.64)	426450 (62.13)
	No	23860 (9.18)	236010 (90.82)	259860 (37.86)
Clinical profile				
Chronic illness (n=694960)	Yes	106520 (25.64)	308780 (74.34)	415310 (59.76)
	No	26050 (9.32)	253610 (90.69)	279650 (40.23)
Anxiety disorders (n=689340)	Yes	43100 (46.21)	50160 (53.78)	93260 (13.53)
	No	88960 (14.92)	507120 (85.08)	596080 (86.47)
Mood disorders (n=689400)	Yes	53970 (57.61)	39710 (42.39)	93680 (13.59)
	No	78220 (13.13)	517500 (86.87)	595720 (86.41)

*Rounded weighted frequency

Table 3.5: Crude odds ratios (with 95% confidence interval) for suicidal ideation

Variable	Category	Odds ratio	95% CI		P-value
			Lower	Upper	
Socio-demographic variables					
Age (Ref: >55 years)	≤ 19 years	0.89	0.69	1.12	<0.0001
	20-34 years	1.45	1.17	1.81	0.0019
	35-54 years	1.71	1.38	2.12	<0.0001
Sex (Ref: Male)	Female	1.45	1.26	1.68	<0.0001
Marital Status (Ref: single)	Married	0.592	0.495	0.707	<0.0001
	Widowed/separated/ or divorced	1.345	1.083	1.670	<0.0001
	Common-low	0.908	0.745	1.107	0.8312
Aboriginal Identity (Ref: Métis)	First Nations	1.26	1.08	1.46	0.2554
	Inuit	1.35	1.13	1.59	0.0220
Level of Education (Ref: Bachelor's degree/ university certificate or diploma or degree above bachelor level)	Grade 8 or lower/some secondary education	1.30	1.01	1.68	0.2596
	Secondary school diploma/some postsecondary education	1.27	0.98	1.64	0.4023
	Postsecondary certificate or diploma below bachelor level	1.29	0.99	1.66	0.3250
Health behavior					
Smoking (Ref: Non smoker)	Daily	2.25	1.93	2.62	<0.0001
	Occasional	1.42	1.11	1.81	0.6388
Alcohol use (Ref: Non drinker)	Occasional	0.95	0.77	1.17	0.3114
	Regular	0.75	0.63	0.89	0.0003
Drug use (Ref: No)	Yes	3.36	2.82	4.01	<0.0001
Clinical profile					
Chronic illnesses (Ref: No)	Yes	3.36	2.88	3.91	<0.0001
Anxiety disorders (Ref: No)	Yes	4.89	4.09	5.87	<0.0001
Mood disorders (Ref: No)	Yes	8.993	7.537	10.729	<0.0001

Table 3.6: Adjusted odds ratios (with 95% confidence intervals) of suicidal ideation

		Model 1	P-value	Model 2 N=640090	P-value	Model 3 N=682740	P-value	Model 4 N=681510	P-value
Diabetes (Ref: No)	Yes	1.36 (1.05-1.77)	0.0193	1.44 (1.09-1.92)	0.0117	1.4 (1.05 – 1.88)	0.0231	1.17 (0.87-1.56)	0.3012
Age (Ref: ≥ 55 years)	≤ 19 years			0.83 (0.57- 1.21)	0.3395	0.74 (0.54-1.00)	0.0527	0.8 (0.58- 1.10)	0.1723
	20-34 years			1.42 (1.07- 1.89)	0.0145	1.07 (0.81-1.41)	0.6407	1.09 (0.84-1.43)	0.5243
	35-54 years			1.83 (1.43-2.34)	<0.0001	1.39 (1.09- 1.79)	0.0089	1.23 (1.01-1.64)	0.0385
Sex (Ref: Male)	Female			1.4 (1.19-1.64)	<0.0001	1.45 (1.25-1.69)	<0.0001	1.17 (1.01-1.37)	0.0430
Marital status (Ref: Married)	Common-low			1.48 (1.18- 1.87)	0.0008	1.22 (0.96-1.55)	0.1018	1.25 (0.98-1.60)	0.0765
	Widowed/ separated/ divorced			2.23 (1.75- 2.83)	<0.0001	1.99 (1.56-2.55)	<0.0001	1.72 (1.33-2.23)	<0.0001
	Single			1.86 (1.49 -2.3)	<0.0001	1.63 (1.32-2.01)	<0.0001	1.52 (1.22-1.89)	0.0001
Aboriginal identity (Ref: Métis)	First Nations			1.16 (1.15- 1.16)	<0.0001	1.13 (1.12- 1.14)	<0.0001	-	-
	Inuit			1.29 (1.08-1.56)	0.0064	1.15 (0.96-1.39)	0.1312	-	-
Education level (Ref: Bachelor's degree/ university certificate or diploma or degree above bachelor level	Grade 8 or lower/some secondary education			1.39 (1.05- 1.83)	0.0197	-	-	-	-
	Secondary school diploma/some postsecondary education			1.33 (1.02- 1.73)	0.0337	-	-	-	-

	Postsecondary certificate or diploma below bachelor level	1.31 (1.02-1.7)	0.0384	-	-	-	-
Smoking (Ref: Non smoker	Daily	-	-	1.61 (1.37-1.89)	<0.0001	1.39 (1.17-1.64)	0.0001
	Occasional			1.15 (0.89-1.49)	0.2875	1.16 (0.88-1.55)	0.2959
Alcohol use (Ref: Non drinker)	Regular	-	-	0.59 (0.49-0.72)	<0.0001	0.71 (0.58- 0.87)	0.0182
	Occasional			0.74 (0.59-0.92)	0.0073	0.76 (0.61-0.96)	0.0007
Drug use (Ref: No)	Yes	-	-	3.34 (2.77- 4.03)	<0.0001	2.82 (2.33-3.42)	<0.0001
Chronic illnesses (Ref: No)	Yes	-	-	-	-	1.73 (1.44-2.07)	<0.0001
Anxiety disorders (Ref: No)	Yes	-	-	-	-	1.52 (1.22-1.88)	0.0001
Mood disorders (Ref: No)	Yes					4.64 (3.77-5.72)	<0.0001
AUC		0.602		0.675		0.768	

Model 1: unadjusted
Model 2: Adjusts for age, sex, marital status, aboriginal identity, and level of education.
Model 3: Adjusts for age, sex, marital status, aboriginal identity, smoking, alcohol use, and drug use.
Model 4: Adjusts for age, sex, marital status, smoking, alcohol use, drug use, chronic illnesses, anxiety disorders, and mental disorders.

CHAPTER- 4: CONCLUSION

This section provides an overview of the study objectives, highlights the methodological approaches used, and offers insight and a brief discussion of the key findings. Finally, it discusses strengths and limitations and notes relevant implications for public health practice and opportunities for future research.

4.1 Overview of study objectives

Diabetes, depression and suicidal behavior are increasingly prevalent conditions with major public health implications (1, 2, 3). A potential association between diabetes, depression, and suicidal behavior has been suggested but not entirely explored (4, 5). Therefore, there is a need for a systematic appraisal of current epidemiological evidence to collectively assess the risk of depression and suicidality in patients with diabetes.

The Indigenous Canadian population is facing a growing epidemic of diabetes, depression and suicidal behavior (6,7). Yet, this vulnerable population is consistently under-represented in research studies that aim to address mental health issues among patients with diabetes. Current knowledge on the extent of the problems of depression and suicidality (specifically, suicidal ideation) among Indigenous diabetic patients is lacking.

Therefore, this thesis aims to address two main objectives: (1) to systematically evaluate the association between diabetes, depression, and suicidal behavior among the general population *(Chapter 2)*; and (2) to assess that inter-relationship between diabetes, depression, and lifetime suicidal ideation among Indigenous Canadians living off-reserve *(Chapter 3)*.

4.2 Methodology and key findings

Chapter 2

A systematic literature review and meta-analysis was conducted to evaluate the risk of depression and suicidality among diabetic patients. Our systematic review methodology closely followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PRISMA is an evidence-based checklist that is used to ensure: (a) transparency of the study selection process; (b) accurate presentation of the study findings; and (c) high quality reporting of the systematic reviews and meta-analyses (8). Five databases were searched for relevant studies. Two reviewers assessed eligibility based on pre-specified inclusion and exclusion criteria to limit the potential for a selection bias. Meta-analysis was used to provide a quantitative synthesis of data and to obtain integrated pooled estimates from the different studies.

A total of 5,750 articles were identified, of those 33 reporting data only on depression, 14 only on suicidality, and three studies reporting data on both depression and suicidality among diabetic patients. Our meta-analysis found that diabetic patients were at a significantly higher risk of depression compared to non-diabetics (p-value <0.001). In cross-sectional studies, among patients with diabetes, the odds of depression were twice as high as those reported in non-diabetics (OR=2.04, 95% CI: 1.73-2.42). Likewise, in cohort studies, the odds of depression in diabetic patients were 1.5 times greater than those of non-diabetics (OR=1.48, 95% CI: 1.36-1.65).

Our meta-analysis also assessed the prevalence of suicidal behavior among patients with diabetes. We found the pooled prevalence of suicidal ideation, attempts, and completed suicide to be 16.2%, 2.7%, and 0.3%, respectively. Additionally, patients with diabetes were at a significantly higher risk for experiencing suicidal ideation (OR of 1.89, 95% CI: 1.36- 2.63) and attempting suicide (OR 1.45, 95% CI: 1.07- 1.96). Finally, there was not enough evidence to support an association between diabetes and suicidal death (OR=1.849, 95% CI: 0.971- 3.519, p-value= 0.061).

Chapter 3

Epidemiological analysis and modeling of secondary data was used to examine the association between diabetes, depressive symptoms, and lifetime suicidal ideation in a national sample of the Indigenous Canadian peoples living off-reserve. In this study, we used data from the Aboriginal Peoples Survey (APS, year 2012), which is a national, cross-sectional survey of Indigenous peoples living off-reserve. A modified version of the K-10 distress scale was used to evaluate depressive symptoms, whereas diabetes and suicidal ideation were self-reported.

In this study, several multivariable logistic regression models were sequentially constructed, where diabetes represented the exposure of interest, while depressive symptoms and suicidal ideation were considered as the main outcomes. These models adjusted for different groups of confounders, which included: socio-demographics, health related behaviors, and clinical profile factors. Meanwhile, the recommended use of weights to statistically adjust our sample resulted in the generalizability of our findings among the Indigenous Canadian population living off- reserve

The total number of Indigenous participants who responded to the depression questions was 963,110. Our study results found the prevalence of depressive symptoms in the Indigenous diabetics to be 15.67% compared to 9.27% among the non-diabetic participants. After adjusting for socio-demographic variables (aOR=1.64, 95% CI: 1.17-2.31), smoking/alcohol use/drug use (aOR=1.53, 95% CI: 1.12- 2.08), anxiety disorders and other chronic illnesses (aOR=1.52, 95% CI: 1.08-2.14), diabetes was still significantly associated with depressive symptoms (p-value= 0.0168).

The total number of Indigenous participants who responded to the suicidal ideation question was 694,960. Our study results found the prevalence of suicidal ideation in diabetics to be 23.86% compared to 18.71% among the non-diabetic participants. After adjusting for the effect of socio-demographic variables (aOR=1.44, 95% CI: 1.09-1.92) and health related behavioral factors (aOR=1.4, 95% CI: 1.05-1.88), diabetes was still significantly associated with a higher risk of reporting suicidal ideation (p-value=0.0231). However, after further adjusting for mental disorders (mood and anxiety) and other chronic illnesses (aOR = 1.17, 95% CI: 0.87–1.56), the association was no longer significant (p-value = 0.3012). It was interesting to note that in our

results, regular use of alcohol had a significant protective effect on both depressive symptoms and suicidal ideation.

4.3 Interpretation of our findings

Chapter 2

Our systematic review and meta-analysis findings reinforce the evidence for an association between diabetes and depression (4, 9). Specifically, our results (based on the included cohort studies) support temporality and suggest a causal association linking diabetes to subsequent development of depression. This finding is not entirely surprising, as there are several plausible psychological and biological explanations that help account for this association. Psychological explanations may include: the demanding nature of diabetes self-management, major lifestyle modifications, and the increased concern among patients of suffering from possible diabetic-related complications and disability (10). Biological contributors may include: activation of the hypothalamic pituitary adrenal axis, changes to blood flow, and chronic inflammation (11, 12).

Our study found that diabetic patients were at a significantly higher risk for suicidal ideation and attempted suicide compared to non-diabetics. The fact that depression is a strong risk factor for suicidality may help explain the increased risk of suicidal ideation and attempted suicide in diabetic patients (13). Still, it is important to highlight that diabetics were more prone to not only consider suicide (suicidal ideation) but also had an increased likelihood to progress to suicidal attempts. This finding is concerning in light of the fact that diabetic patients have ready access to anti-diabetic medications that could be (mis)used as a means of committing suicide. However, it should be noted that our study found no difference in the risk for completed suicide between diabetic and non-diabetic individuals. This finding may be attributed to several factors, including: (a) the many barriers to accurate assessment and reporting of suicidal deaths; and (b) the possibility that predictors of suicidal ideations may be different from those associated with suicidal death.

Chapter 3

Our study found that Indigenous diabetic patients were at a significantly higher risk for depressive symptoms and suicidal ideation compared to non-diabetics. The strength of this association was maintained even after adjusting for several confounders, suggesting that these factors could not fully account for the co-occurrence of diabetes, depressive symptoms and suicidal ideation. These results are concerning, especially when considering that Indigenous diabetic patients are under-screened and under-treated for depression in primary healthcare settings (14,15). This finding may be better understood within the historical context and socio-political struggles of the Canadian Indigenous peoples. Among those factors, the disadvantageous socio-economic conditions and traumatic historical experiences (e.g. residential schools) have played a critical role in causing severe heath disparities and may be associated with a higher risk of diabetes, depression and suicidal behavior among Indigenous peoples. Further research into the links of these important and culturally sensitive health topics is needed.

In this study, differences in mental disorders (anxiety and mood) and chronic illnesses accounted for the increased risk of suicidal ideation among diabetics. This may be due to the fact that diabetes is associated with a much higher burden of mental disorders and chronic illnesses (16,17). Therefore, mental disorders and chronic illnesses can act as mediating factors in the pathway of the association between diabetes and suicidal ideation.

In our results, there was an indication of a protective effect for regular alcohol use against depression and suicidal behavior. Some suggestions to explain this effect include: (a) a direct protective effect for alcohol; and (b) the social aspects involved in alcohol drinking may enhance the psychological well-being of moderate regular drinkers compared to abstainers (18). However, this finding should be interpreted with caution, as some key details in alcohol use were not available (i.e. frequency, volume, duration), which can significantly modify the association between alcohol use, depression and suicidal behavior.

Comparative findings

Comparing findings from our cross-sectional study (assessing Indigenous participants) to the systematic review and meta-analysis (reflective of the general population) yielded some additional important outcomes. The risk of depressive symptoms among Indigenous diabetic individuals (OR= 1.82) was relatively higher than the one calculated in our subgroup meta-analysis (based on the cross-sectional studies assessing depressive symptoms) (OR=1.47). Given the novelty of the tool used to evaluate depressive symptoms in our study, the findings may not be generalizable. However, it is also likely that Indigenous diabetic individuals may suffer a higher burden of depression compared to the general diabetic population, possibly due to the associated health disparities and socio-political struggles faced by this vulnerable population.

Surprisingly, the risk of suicidal ideation among our Indigenous diabetic study participants (OR= 1.36) was relatively lower than the one calculated among the general population in our meta-analysis (OR=1.89). To understand this finding, one needs to consider several factors, which may include differences: (a) in the suicidal ideation assessment tools used by the various studies, (b) in the assessment period between our meta-analysis studies (assessed short-term suicidal ideation from two to four weeks) and our cross-sectional study (assessed lifetime suicidal ideation); (c) in the social perception, negative stereotypes and stigmatization associated with the Indigenous peoples and suicidal behavior. To examine this possibility, an additional (post-hoc) analysis was conducted, where we found that Indigenous diabetic patients were more likely to skip or refuse to answer the suicidal ideation question compared to non-diabetic participants. Thus, additional research is needed to explore this culturally sensitive and complex topic.

4.4 Strengths and Limitations

Chapter 2

The major strengths of our systematic review and meta-analysis are reflected in its collective examination of depression and suicidality as outcomes of interest and the statistical evaluation of a variety of factors among 50 studies. The most prominent limitations centered on the statistical heterogeneity between studies and the small number of studies that specifically assessed suicidality.

Chapter 3

The major strengths of our secondary analysis were the use of a large national sample of the Indigenous Canadian population and the construction of sequential multivariable models. Modeling was used to help examine the independent association between diabetes, depressive symptoms and suicidal ideation while adjusting for a variety of factors (socio-demographic, health related behavior, and clinical profile variables). The most prominent limitations centered on the use of self-report data, which may lead to under or over-reporting of responses and the lack of validation studies for our modified K-10 scale (used to assess depressive symptoms), which may impact the generalizability of our findings.

4.5 Implications for public health practice

Chapter 2

Although the problems of depression and suicidal behavior in patients with diabetes are serious and concerning, significant improvements can be made using integrative interventions that create a multifaceted partnership between diabetic patients, healthcare providers, policy makers, and the healthcare system. It is reported that the majority of diabetic patients are mainly seen and managed in primary care settings. However, it has been shown that comprehensive depression screening and treatment in these settings occurs infrequently and is less than optimal (19). This is due to the fact that diabetic patients and healthcare providers mutually prioritize addressing the physical health needs first and foremost rather than mental health (14).

Therefore, health promotion initiatives among diabetic patients should focus on reducing mental health stigma and raising awareness on the importance of discussing their mental health concerns during regular follow-up visits with their physicians. Training of primary healthcare providers is crucial to: (a) overcome poor knowledge and increase awareness of the common co-occurrence of diabetes, depression and suicidal behavior; and (b) familiarize them with depression and suicidal behavior screening tools and management strategies. Policy makers and clinical practice recommendations need to emphasis the importance of regular psychological screening especially for high-risk groups such as diabetics. The healthcare system should work on: (a) integration of services and improvement of referral networks; and (b) enhancing the role of nurses and allied

healthcare professionals in mental health services, especially in remote and rural areas.

Chapter 3

Despite the high rates of depression and suicidal behavior among Indigenous Canadian diabetics, they are less likely to seek mental health services. Indigenous patients lack trust in the western mainstream approaches to medical management and treatment of many diseases, including diabetes and mental disorders. Additionally, mainstream medical approaches ignore the holistic Indigenous view of health and wellness. Therefore, integration of traditional Indigenous knowledge should be a key component in all interventions targeting the health of Indigenous peoples.

Similarly, healthcare providers should seek to receive culturally appropriate training to improve their communication skills with Indigenous patients. The healthcare system should support collaboration with community leaders and engagement of communities to build trust and increase knowledge about the high risk of depression and suicidal behavior among Indigenous diabetic patients. Finally, given the complexity of the problem of depression and suicidal behavior among Indigenous diabetic patients, collaborative and interdisciplinary efforts aimed at early identification and management may help improve treatment outcomes and decrease the disability associated with these conditions.

4.6 Future research

Chapter 2

Identification of modifiable risk factors that contribute to the associations between diabetes, depression and suicidal behavior would help in the design and development of comprehensive intervention strategies. Research that focuses on the characterization of distinctive predictive factors for suicidal death, in addition to suicidal ideation or attempts is warranted.

Chapter 3

Future research is needed to examine the associations between diabetes, depression and suicidality among the Indigenous Canadian population living on-reserve. Research that assesses the correlation between the modified K-10 scale (used in our study) and the clinical diagnosis of depressive disorders is required. Since this scale represents a new tool that is short, easy to administer, and shown to be acceptable among Indigenous peoples, it could potentially be used for depression screening in primary healthcare settings. Finally, there is a need to examine the role and mechanism of diabetes in the development and progression of depression and suicidal behavior both in the general and the Indigenous Canadian population.

4.7 Conclusion

This thesis addressed an important and yet under-investigated research topic concerning the association between diabetes, depression, and suicidal behavior. It used different sets of analytical tools and investigative methods (systematic review and meta-analysis and secondary data analysis) to evaluate the associations of interest both in the general and the Indigenous Canadian populations. We found that diabetic patients were at an increased risk for depression and suicidal behavior compared to non-diabetics.

Integrative, multifaceted interventions that involve diabetic patients, healthcare providers, and the healthcare system are needed. Implementation of effective screening and management strategies for depression and suicidal behavior among Indigenous peoples and the wider population could help mitigate their negative impact on a diabetic patient's quality of life and reduce the growing burden on the healthcare system. It is important to note that this research work is exploratory in nature and may act as an early step in elucidating a plausible link between these highly prevalent conditions.

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APPENDIX 1- NEWCASTLE OTTAWA QUALITY ASSESSMENT SCALE

A. Case-control Studies

Note: A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition of depression or suicidality adequate?
   a) Yes, with clinical evaluation, ICD code, or record linkage*
   b) Yes, based on supervised self-reports (questionnaires)*
   c) Based on unsupervised self-report
   d) No description

2) Representativeness of the cases of depression and suicidality
   a) Consecutive or obviously representative series of cases*
   b) Potential for selection biases or not stated

3) Selection of Controls
   a) Community controls*
   b) Hospital controls
   c) No description

4) Definition of Controls
   a) No history of depression (endpoint)*
   b) No description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) Study controls for demographic variables*
   b) Study controls for any additional factor*

Exposure

1) Ascertainment of exposure
   a) Secure record (e.g. medical records)*
   b) Structured interview where blind to case/control status or lab test*
   c) Interview not blinded to case/control status
   d) Written self-report or medical record only
   e) No description

2) Same method of ascertainment for cases and controls
   a) Yes*****
   b) No

3) Non-Response rate
   a) Same rate for both groups*****
   b) Non-respondents described
   c) Rate different and no designation

Quality rating	**Selection Domain**	**Outcome Domain**	**Comparability**
Good	≥3	3	2
Fair	1-2	2	1
Poor	0	0-1	0

B. Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) Truly representative of the average diabetic in the community*
   b) Somewhat representative of the average diabetic in the community*
   c) Selected group of users e.g. nurses, volunteers
   d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort*
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure (diabetes)
   a) Secure record (e.g. medical records) or lab tests*
   b) Structured interview*
   c) Self-report
   d) No description

4) Demonstration that depression or suicidality (ideation or attempts) were not present at start of study
   a) Yes*
   b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) Study controls for demographic variables*
   b) Study controls for any additional factor*

Outcome

1) Assessment of outcome
   a) Clinical diagnosis*
   b) Record linkage*
   c) Structured interview or supervised questionnaire*
   d) Self-report (questionnaire)
   e) No description

2) Was follow-up long enough for outcomes to occur?
   a) Yes (1 yr.)*
   b) No

3) Adequacy of follow up of cohorts
   a) Complete follow-up - all subjects accounted for*
   b) Subjects lost to follow up unlikely to introduce bias - small number lost - > 20 follow up, or description provided of those lost)*
   c) Follow-up rate < 80% (select an adequate %) and no description of those lost
   d) No statement

Quality rating	**Selection Domain**	**Outcome Domain**	**Comparability**
Good	≥3	3	2
Fair	1-2	2	1
Poor	0	0-1	0

C. Cross-sectional Studies

Selection

1) Representativeness of the exposed (diabetic) group

a) Truly representative of the target population in the community*
b) Somewhat representative of the target population in the community*
c) Selected group of users e.g. nurses, volunteers
d) No description of the derivation of the group

2) Ascertainment of exposure (diabetes) status

a) Secure record (e.g. medical records) or lab tests*
b) Structured interview*
c) Written self-report
d) No description

3) Demonstration that outcome of interest was not present at start of study

a) Yes*
b) No

Outcome

1) Assessment of outcome

a) Clinical diagnosis*
b) Record linkage*
c) Structured interview or applied questionnaire*
d) Self-report (questionnaire)
e) No description

2) Completeness of outcome measure across groups

a) Complete outcome measures for all subjects (not greater than 5% missing)*
b) Missing outcome measures handled with appropriate methods e.g. imputation*
c) > 5% outcome data missing with no description of how it was handled

Quality rating	Selection Domain	Outcome Domain
Good	≥2	2
Fair	1	1
Poor	0	0

INDIVIDUAL STUDY DECISION

Study Risk of Bias	**Domain**
Low	Good quality in all domains
Unclear/moderate	Fair quality in one or more domains without Poor quality
High	Poor quality in any domain